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THROMBOTIC THROMBOCYTOPENIC PURPURA

Report of a Case, with a Review of the Pathogenesis of the Disease

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THROMBOCYTOPENIC purpura, anemia and manifestations of severe involvement of the central nervous system constitute the clinical triad of thrombotic thrombocytopenic purpura.[1,2] Fibrinoid "degeneration" of the arterioles and capillaries, without inflammatory changes, and eventual bland thrombosis of the affected vessels form its histologic counterpart.[3-5] Polyvalent immunoallergic mechanisms still unproved have been suspected of causing this disease.[6,7]

The purpose of this paper is to report another case of thrombotic thrombocytopenic purpura in which the signs of cortical irritation with epileptiform seizures were associated with electroencephalographic changes and overshadowed the anemia and bleeding tendency and led to a diagnosis of possible brain tumor. We wish also to emphasize the diffuse arteriocapillary changes that, in the absence of an inflammatory component, separate this syndrome from the large group of necrotizing angiitides as described by Zeek.[8,9]

CASE REPORT

A 27-year-old shoemaker of Armenian descent was admitted to Worcester City Hospital for the 1st time on October 24, 1955, in a semicomatose state after a convulsive seizure that had occurred in a bowling alley. There was no past history of seizures or epilepsy. One week previously he had had diarrhea for 3 days; otherwise he was well until the day of admission. As a child he had frequently complained of dizziness and poor eyesight, which deferred him from military service.

Physical examination revealed a well developed, well nourished man in a semicomatose state. Multiple ecchymotic areas were present on the skin of the shoulder, arms and left cheek. There was no lymphadenopathy. Examination of the chest and lungs was negative. The heart was not enlarged and exhibited a regular sinus rate. The abdomen was obese. Neurologic examination disclosed equal pupils reacting to light. The neck was supple. The cranial nerves appeared intact. The tendon reflexes were symmetrical and hyperactive; the plantar reflexes were physiological.

The temperature was 101°F., the pulse 92, and the respirations 24.

Lumbar puncture showed an initial spinal-fluid pressure equivalent to 300 mm. and a final pressure equivalent to 265 mm. of water. The fluid was crystal clear.

Examinations of the blood disclosed a hemoglobin of 9.7 gm. per 100 ml. and a white-cell count of 8000, with 36 per cent lymphocytes, 4 per cent monocytes, 1 per cent eosinophils and 1 per cent nonsegmented and 58 per cent mature neutrophils. The spinal fluid contained 2 lymphocytes per cubic millimeter; the spinal-fluid sugar was 71 mg., and the total protein 60 mg. per 100 ml. Culture of the spinal fluid was negative.

The patient was placed on barbiturates. He remained in a postconvulsive coma for 2 days. An electroencephalogram showed abnormal waves consistent with a seizure disorder. At the patient's insistence he was discharged on October 27. Two days later he was readmitted to the hospital in coma, with a history of having had a convulsive seizure while reclining at home. On admission a slight icterus of the scleras was noted. He was deeply comatose and hyperpneic but the neck was supple. The remainder of the physical examination was negative.

The pulse was 120, and the respirations 36. The blood pressure was 170/100.

A repeat spinal tap showed clear cerebrospinal fluid under a pressure equivalent to 265 mm. of water.

Shortly after admission Cheyne–Stokes respirations developed, and the patient had a recurrence of the seizures, which appeared to be predominantly right sided. The temperature rose to 105°F.; the blood pressure dropped to 90/50. He was taken to the operating room, where a ventriculogram revealed a slight bulging of the 3d ventricle. He died on the operating table.

At autopsy the body was that of a well developed, well nourished man measuring 185 cm. in length and weighing an estimated 100 kilograms. The skin was of normal color. Large ecchymotic areas, appearing a few days old, were present on the right shoulder, right arm and left arm. No enlarged lymph nodes were noted; 120 ml. of dark-yellow, clear pericardial fluid was present in the pericardial sac. The heart weighed 500 gm. The epicardium displayed numerous petechiae, more pronounced along the posterior wall of the right chambers. No fibrinous pericardial exudate was present. Petechiae were also seen on section of the right myocardium and under the endocardium of the right chambers. The valves were thin, delicate and competent. The coronary vessels showed a minimal degree of arteriosclerotic change.

The right lung weighed 550 gm., and the left 650 gm. The pleural surfaces displayed no petechiae. The parenchyma was markedly congested.

The spleen weighed 260 gm. The capsule was smooth. The pulp was magenta in color and softer than normal, with malpighian bodies standing out clearly.

Examination of the gastrointestinal tract displayed no gross abnormalities. The appendix was absent.

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The liver weighed 2500 gm. Its surface was smooth, and the cut section showed a normal lobular architecture, with a diffuse yellow hue.

The gall bladder and pancreas were normal. The adrenal glands were smaller than normal and without significant changes grossly in the cortex or medullary areas.

The left kidney weighed 180 gm., and the right 190 gm. The renal parenchyma was noted to be softer than normal, but otherwise displayed no unusual gross features.

The ureters, prostate and bladder were grossly normal. Both testes were markedly atrophic, consisting on section of homogeneous yellow-brown soft tissue.

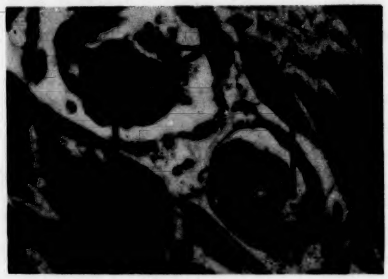

FIGURE 1. *Section of the Heart, Showing an Early Bimorphic Thrombus, Platelet Thrombus* (A) *and the Eosinophilic Material* (B) *in the Vessel Wall (Hematoxylin and Eosin Stain X220).*

Note the absence of inflammatory changes in the vessel wall and in the surrounding myocardium.

The organs of the neck showed no gross abnormalities.

The brain weighed 1410 gm. No exudate or hemorrhage was present in the meningeal spaces. Both hemispheres were symmetrical. There was no evidence of increased intracranial pressure. The gyri were not flattened, and the sulci appeared normal. Serial sections showed rare petechial hemorrhages situated in the left frontal region of the cerebrum and in the brain stem. The pineal and pituitary glands were grossly normal.

On microscopical examination representative specimens of tissue were sectioned and stained routinely with hematoxylin and eosin and as indicated with periodic acid Schiff, van Gieson and Mallory's phosphotungstic acid hematoxylin. The epicardium of the right ventricle showed areas of hyalinization in the loose reticulum underlying the mesothelial cells. The latter layer of cells was intact but was high cuboidal in shape. Erythrocytes and aggregations of lymphocytes were occasionally encountered in the epicardial fat. Miliary infarcts were seen in all sections of the myocardium; some were recent and hemorrhagic and accompanied by an acute inflammatory reaction. Others were healing and composed of granulation tissue interspersed with pigmented macrophages, lymphocytes and a few eosinophilic granulocytes. The infarcts tended to be situated in the subepicardial myocardium. The interstitial tissue, especially in the right myocardium, was very edematous and contained fibrin, red cells and leukocytes. The valves showed no vascularization or increased cellularity. The endocardium except for a few petechiae was normal. Many arterioles showed eccentric accumulations of smudgy eosinophilic material and, in many areas, intraluminal swelling and formation of small verrucal lesions that were either covered by an intact endothelium or capped by a light eosinophilic granular substance (Fig. 1). These changes were not associated with an inflammatory reaction. Many capillaries and venules contained granular thrombi. Other vessels showed organization of the lesions by proliferating endothelial cells. The vessels of the lungs were engorged, and the alveoli were filled with a pink fluid containing a few granulocytes. Rare granular thrombi were seen in the capillaries of the alveolar wall; 2 or 3 megakaryocytes per low-power field were seen in the pulmonary capillaries. The red pulp of the spleen was markedly congested, with many hemosiderin-laden macrophages present. The malpighian bodies displayed large, active germinal centers. Occasional arterioles showed fibrillar changes. The walls of the veins and trabeculae were free of inflammation. The liver demonstrated considerable fatty change, without fibrosis or focal necrosis. No alcoholic hyaline was seen. A few hepatic arterioles had fibrinoid changes similar to those described in the heart. The interlobular arteries and afferent glomerular arterioles of the kidneys were dilated and partially occluded by masses of eosinophilic material that in places was smudgy and in others more granular in appearance. Vascular changes extended occasionally into the tufts. A few tubules showed red-cell casts associated with intraepithelial granules of hemosiderin. Vascular changes in the adrenal blood vessels were severe and resembled those found in the heart. Associated petechiae and focal necrosis were present in the cortex.

Similar vascular changes without alteration of the parenchymal stroma were seen in the sections of lymph nodes, diaphragm, pancreas and thyroid gland. The testes were markedly atrophic. The interstitial cells were hyperplastic, forming large lobules surrounded by fibrous tissue and the atrophic elements of the testicles (Fig. 2). Vascular changes were pronounced and consisted of accumulations of hyaline, vacuolated, periodic-acid-Schiff-positive material eccentrically placed in the walls of the arterioles. This material was apparent just under the intima of some vessels, and in others it involved the entire thickness of the wall. As the lesions increased in size the material became more smudgy and more granular and formed sessile intraluminal masses.

FIGURE 2. *Section of the Testes (Periodic-Acid-Schiff Stain X60).*

At the left are hyperplastic interstitial cells (A). *Atrophic hyalinized tubules are present on the right* (B). *Note the vascular changes characterized by eccentric subintimal accumulation of periodic-acid-Schiff-positive material.*

Examination of the vertebral bone marrow revealed erythroid and megakaryocytic hyperplasia. Approximately 16 megakaryocytes per low-power field were seen, many young forms being present. A few vessels contained granular thrombi.

Examination of the central nervous system included sections from the left frontal region, central nuclei, midbrain, pons, medulla oblongata and hippocampus. In all sections examined the vascular changes described above were pronounced and were associated with the presence of red cells in the Robin–Virchow spaces. Minimal alterations in the histologic pattern of both white and gray matter were observed. These changes, which were most striking in the brain stem, consisted of perivascular proliferation of glial cells, loosely packed polymorphic microglial cells, a few astrocytes and oligodendroglial cells (Fig. 3). The neurons displayed a loss of Nissl substance, with pallor of

the nuclei and with complete dissolution of the neurons in some areas. Eosinophilic smudgy material was present not only in the capillaries of the choroid plexus but also in the loose intervascular supporting tissue. Vascular changes were also found in the pituitary and pineal glands.

Discussion

The presence of hyaline material eccentrically placed in the subintima of arterioles and capillaries without a significant inflammatory reaction constitutes the histologic hallmark of thrombotic thrombocytopenic purpura. The first recognizable histologic change consists of a focus of smudgy eosinophilic material under the intima of the affected vessels.[3] At this stage no reaction of the endothelium is noted. Intraluminal swelling of the eosinophilic material forms small verrucae covered by endothelium. This endothelial covering may rupture. When platelets are deposited at the site of rupture the bimorphic thrombus described by Gore[3] is formed. This lesion consists of two parts: a base of smudgy eosinophilic material extending from the walls of the arterioles into the lumen and an intraluminal cap of lighter eosinophilic granular material representing the agglutinated platelets. Eventually, the thrombotic process becomes organized by the invasion of proliferating

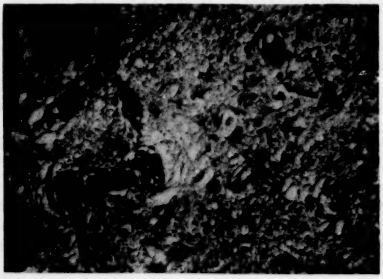

Figure 3. *Section of the Midbrain through the Inferior Colliculi, Showing Marked Vascular Alterations, with Minimal Changes in Surrounding Tissue (Hematoxylin and Eosin Stain X60).*

In the right upper field (A) *there is a perivascular glial reaction with polymorphic microglia.*

endothelial cells. The histologic changes in the parenchyma of organs containing these vascular lesions are usually minimal, ranging from petechiae to minute infarcts. Diffuse involvement of the vessels of the central nervous system is the most probable explanation for the rapid course of the disease, with a fatal termination.

The mild histologic appearance of these lesions differs strikingly from the violent inflammatory reaction seen in the necrotizing angiitides. As described by Zeek,[9] the necrotizing angiitides, whether in arteries, capillaries or veins, are characterized by an inflammatory reaction and fibrinoid necrosis. Periarteritis nodosa, hypersensitivity angiitides, rheumatic arteritis and temporal arteritis fall into this category. They differ from one another in the location of the lesion in the vascular tree, and in the presence or absence of associated granulomatous inflammation involving the extravascular collagen. That such lesions can be the result of hypersensitivity has been shown by Rich.[10,11] The absence of inflammation regularly noted in thrombotic thrombocytopenic purpura suggests a different pathogenesis.

Hemolytic anemia, thrombocytopenia and vascular injury have all been produced by abnormal immunologic mechanisms. These conditions are present in thrombotic thrombocytopenic purpura, and for this reason the disease has been suspected of being produced by such mechanisms. The hemolytic process is always present in this syndrome and has been investigated in detail by Singer, Motulsky and Shanberge,[12] who showed that the shortened life span of red cells was caused by an extracorpuscular mechanism. The Coombs test has regularly been recorded as negative. This suggests either that the hemolytic process is not mediated by globulin or that the hemolytic agent does not become fixed to the surface of the red blood cells.[13]

A potent platelet agglutinin has been isolated by Stefanini et al.[14] in a case of idiopathic thrombocytopenia. This agglutinin acted not only on circulating platelets but also on megakaryocytes and the platelets forming on their surfaces. The authors believe that the agglutinin demonstrated was an antibody, for it could be removed from the patient's plasma by repeated absorption with packed platelets. Furthermore, the platelet Coombs test was positive, and the transfusion of the patient's plasma into healthy recipients resulted in thrombocytopenia and morphologic changes of the megakaryocytes similar to those seen in idiopathic thrombocytopenic purpura.

Ackroyd[15] showed that Sedormid (allylisopropylacetylcarbamide) may be adsorbed by platelets and endothelial cells, which are thus altered and become weak antigens. In recipients who formed antibodies to the drug thrombocytopenic purpura developed whenever it was readministered. An extrinsic type of platelet destruction similar to those operative in autoimmune hemolytic anemia was believed to have occurred in these 2 cases.

The cause of thrombocytopenia in thrombotic thrombocytopenic purpura still remains obscure. Adelson et al.[7] reported a shortened platelet survival time in 2 of their cases but were unable to demonstrate platelet agglutinin. It has been shown, however, that platelets are destroyed when utilized,[16] so that a shortened survival time may be an index of increased platelet removal.

The existence of endothelial antibodies has been substantiated by the work of Clark and Jacobs,[17] who produced vascular purpura in dogs after injections of

rabbit antiserum prepared from endothelial lining of dog aorta. The authors noted no change in the hemogram. The Henoch–Schönlein syndrome (non-thrombocytopenic purpura) may be explained by such a mechanism. Streptococcal infections usually antedate the appearance of purpura, both in thrombotic thrombocytopenic purpura and in the Henoch–Schönlein syndrome, by ten or fifteen days, which is the approximate interval between the administration of serum and the appearance of the signs of serum sickness. ACTH, furthermore, has been shown to inhibit antibody production.[18] Stefanini et al.[19] have reported the favorable action of ACTH in the Henoch–Schönlein syndrome on the clinical course of the disease and on the vascular changes as demonstrated by repeat biopsies.

The presence of vascular antibodies, which would shed considerable light on the pathogenesis of thrombotic thrombocytopenic purpura, has not yet been reported.

In summary, immunohematologic disorders involving red cells, platelets, megakaryocytes and endothelial cells have not been demonstrated in thrombotic thrombocytopenic purpura although these mechanisms have been highly suspected because of their occurrence in clinically related diseases.

Vascular injury is one of the characteristics of the Schwartzman phenomenon[20]; Gore[3] rejected this mechanism as operative in thrombotic thrombocytopenic purpura, believing the Schwartzman phenomenon to occur only on the venous side of the vascular tree. He also considered the inflammatory component to be a significant feature of the phenomenon. However, intravenous injection of both preparatory and provocative doses of antigen produces characteristic cortical necrosis of the kidney, which results from both arteriolar and capillary thrombosis.[20] Schwartzman, Klemperer and Gerber[20] also demonstrated that in some cases biopsy taken at the site of preparatory injection before the administration of the provocative dose showed a perivascular leukocytic infiltration. The inflammatory component in this phenomenon does not appear to be specific but appears to be secondary to the direct action of the toxin or its vehicle. Vascular injury with thrombosis appears to be the essential feature of the Schwartzman phenomenon.

Schwartzman showed that the increased vascular permeability was important for the production and localization of this phenomenon. It is interesting in this regard that the patient described in this report showed severe atrophy of the testicles, with hyperplasia of the interstitial cells; this feature was also noted in the case described by Popper and Kushner.[21] Steroids[22] have been shown to influence vascular permeability. Humble[23] has demonstrated that the point of bleeding in the cases of purpura is at the arteriolar capillary junction. It is this segment of the vascular tree that appears to be the most vulnerable to a circulating toxin. This segment is regularly involved in thrombotic thrombocytopenic purpura.

Utilizing the Schwartzman phenomena, Brunson, Thomas and Gamble[24] have produced lesions histologically similar to those found in thrombotic thrombocytopenic purpura. The injection of meningococcal endotoxin in rabbits causes lesions characterized by the deposition of fibrinoid material in the intima of arterioles. This material stained like fibrinoid but was digested by trypsin. The resistance of fibrinoid to digestion is considered one of its identifying characteristics.[25] Brunson et al.[26] advanced the hypothesis that the material was derived from the circulating blood and probably represented fibrinogen altered by the injection of endotoxin. These lesions are histologically similar to those found in thrombotic thrombocytopenic purpura. However, the material found in the vessels of thrombotic thrombocytopenic purpura is resistant to digestion by trypsin[27] and thus differs from the lesions produced by Brunson et al. The significance of this difference in the reaction of trypsin is not apparent.

Summary and Conclusions

The basic pathologic changes in thrombotic thrombocytopenic purpura are reviewed.

The lesions in thrombotic thrombocytopenic purpura and its pathogenesis are compared to the necrotizing angiitides.

The lesions differ markedly from the group of hypersensitivity angiitides chiefly in the absence of an inflammatory reaction. The resemblance of thrombotic thrombocytopenic purpura to immunologic disorders is discussed.

The Schwartzman phenomenon cannot be disregarded as a mechanism operative in the production of thrombotic thrombocytopenic purpura. The localization of lesions appears to be related to vascular permeability.

Lesions similar to those of thrombotic thrombocytopenic purpura have been produced experimentally by means of the Schwartzman phenomenon. These lesions, however, differ from those found in thrombotic thrombocytopenic purpura in that the material contained in the arteriolar walls is not resistant to trypsin whereas the material found in cases of thrombotic thrombocytopenic purpura is resistant to trypsin digestion.

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EPISODIC STUPOR FOLLOWING PORTACAVAL SHUNT*

Observations on Etiology and Therapy

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SINCE the report of Gabuzda et al.[1] of episodes of "impending coma" in patients with hepatic cirrhosis given ammonium-containing cation-exchange resins, and the studies of Phillips et al.[2] on the precipitation of this syndrome by the ingestion of nitrogenous substances, the role of ammonia in hepatic coma has been extensively explored. As a result of these investigations the restriction of dietary protein has been recommended as a therapeutic measure in patients with hepatic cirrhosis in whom impending coma or stupor develops.

The association of elevated blood ammonia with episodes of stupor occurring in several patients with portacaval shunts has also been reported in recent years.[3-6] These reports have emphasized the deleterious role of a high-protein intake in this type of stupor. In view of the importance of the recognition and treatment of this syndrome in patients who have had shunts performed, we are describing the effects of the ingestion of various amounts and types of protein, of oral administration of ammonium chloride, of protein hydrolysate infusions and of neomycin by mouth upon mental status and venous blood ammonia concentrations§ in a patient with hepatic cirrhosis and a portacaval shunt.

CASE REPORT

A 58-year-old man was admitted to Syracuse University Hospital in a stuporous state on May 9, 1955.

He was first admitted to the hospital, with hematemesis, in September, 1954, when a diagnosis of portal cirrhosis with bleeding esophageal varices was made. He had a history of chronic alcoholism associated with a poor dietary intake for many years. A splenorenal shunt was performed.

In March, 1955, he was readmitted to the hospital with gastrointestinal bleeding. X-ray study again revealed the presence of esophageal varices. On March 30 a portacaval shunt was performed. He was discharged on April 12.

On April 25 he was readmitted to the hospital in a comatose state. Physical examination revealed a Babinski reflex on the right side not associated with other signs of pyramidal-tract disease. Pneumonitis of the left lower lobe was also present. Initially, he was treated with fluids parenterally, and later given a low-protein formula by tube combined with 4 gm. of neomycin daily. Recovery of consciousness was complete in 5 days. At that time it was not known whether this represented a cerebral thrombosis or hepatic coma. He was discharged on May 6, on a diet containing 3000 calories and 60 gm. of protein.

On the evening of May 7 he ingested a high-protein meal; on May 8 he was able to eat breakfast, but shortly there-

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§The blood ammonia was determined by a modification of the method of Conway,[4,7] analyses being carried out with a ten-minute diffusion period that was begun three minutes after the blood was drawn. The average value in normal persons is 31 microgm. of ammonia nitrogen per 100 ml., with a range of 10 to 50 microgm. per 100 ml.

after increasing confusion developed and was associated with twitching movements of the lower extremities. Twenty-four hours later he was taken to the emergency room in deep stupor.

The past history revealed that in 1941 he had had positive blood and spinal-fluid Wassermann reactions and was treated with malaria injections. In September, 1953, the serologic test was still positive, and he received 15,000,000 units of penicillin.

Physical examination showed a well developed, almost emaciated, semiresponsive man. He appeared somewhat dehydrated. The right pupil was larger than the left, and neither pupil reacted to light. The ocular fundi were unremarkable. Examination of the ears, nose and throat was unremarkable aside from poor oral hygiene. The neck was somewhat stiff. The lungs were clear. The heart was not enlarged, and there were no murmurs. Examination of the abdomen revealed well healed surgical scars in the epigastrium and right upper quadrant. A firm, smooth liver was palpable 3 cm. below the right costal margin. The bladder was distended to the level of the umbilicus. Normal bowel sounds were present, and there was no abdominal tenderness or spasm. The examination of the extremities, genitalia and rectum was within normal limits. No localizing neurologic signs were noted, nor were any pathological reflexes present.

The temperature was 96.6°F., the pulse 68, and the respirations 18. The blood pressure was 160/100.

The hemoglobin was 14.5 gm. per 100 ml., the hematocrit 43 per cent, and the white-cell count 5000, with 33 per cent neutrophils, 65 per cent lymphocytes and 2 per cent eosinophils. The urine was yellow and alkaline, with a specific gravity of 1.020 and negative tests for albumin and sugar. The blood serologic test was negative. The nonprotein nitrogen was 32 mg., and the fasting blood sugar 63 mg. per 100 ml. Examination of the spinal fluid revealed 4 or 5 mononuclear cells per cubic millimeter and a +++ serologic titer for syphilis. Liver-function studies are shown in Table 1.

Liver biopsy performed on September 16, 1954, revealed nodular architecture and fibrosis consistent with Laënnec's cirrhosis. Three months after the portacaval shunt was performed a repeat biopsy (performed on June 21, 1955) showed a nodular pattern, with broad zones of portal fibrosis and marked chronic inflammatory changes consistent with advanced portal cirrhosis. These changes were more advanced than those of the previous biopsy.

During the first 83 days in the hospital the patient had 7 episodes of deep stupor or coma that followed various measures described in Figures 1 and 2. Subsequently, he received neomycin for 54 days, during which he had only 1 episode of stupor. This followed the administration of ammonium chloride and lasted for 48 hours (Fig. 3). Furthermore, he was able to tolerate a diet of 90 gm. of protein daily. On September 22 he was discharged with instructions to take neomycin at home. Four days later he was readmitted to the hospital in stupor, apparently having failed to take the medication. The hospital course during this readmission is shown in Figure 4. Neomycin therapy was reinstituted, with restoration of normal mental status in 7 days. During this admission 2 brief episodes of stupor occurred concurrent with intravenous administration of protein hydrolysate solution. A final episode of coma followed the withdrawal of neomycin for the 2d time, and despite reinstitution of this therapy, with subsequent reduction of blood ammonia levels, he died on November 12.

Autopsy revealed a small amount of straw-colored fluid in the peritoneal cavity. The portacaval anastomosis was patent, with no evidence of occlusion. Examination of the splenorenal shunt revealed a fibrotic, cordlike structure in which no lumen could be found. The spleen was absent. The liver weighed 600 gm. and was greatly contracted and distorted. The external surface was knobby and had a tawny appearance. The esophagus contained several varices in the lower third, but no area of erosion or hemorrhage was detected. The right lung weighed 1200 gm., and the left 900 gm. The posterior portion of all 3 lobes of the right lung were consolidated. The basilar portions of both lobes of the left lung revealed the same lesion, to a lesser degree. The remainder of the examination was noncontributory.

TABLE 1. *Liver-Function Studies.*

DATE	BROMSULFALEIN RETENTION	SERUM BILIRUBIN			THYMOL TURBIDITY*	PROTHROMBIN	URINARY UROBILINOGEN†	CEPHALIN FLOCCULATION	SERUM ALBUMIN	SERUM GLOBULIN	TOTAL PROTEIN
	IN 45 MIN.	DIRECT	INDIRECT	TOTAL			IN 2 HR.				
	%	*mg./100 ml.*	*mg./100 ml.*	*mg./100 ml.*	*units*	*% of normal*	*Ehrlich units*		*gm./100 ml.*	*gm./100 ml.*	*gm./100 ml.*
May 17					30	100			3.0	3.3	6.3
May 18	20										
May 20		0.0	0.5	0.5	56		0.8				
May 23							0.4				
May 31		0.2	0.3	0.5	71		1.4				
June 6					15						
June 8	24				25						
July 1					18				2.7	3.4	6.1
July 5					17						
July 11							0.8				
July 13									2.5	3.7	6.2
July 21									2.8	3.0	5.8
Aug. 1		0.1	0.5	0.6		90					
Aug. 3								++			
Nov. 11		0.0	0.9	0.9		50			2.3	2.9	5.2

*Normal, less than 30 units.
†Normal, less than 1.3 Ehrlich units/2 hr.

DISCUSSION

As shown in Figures 1-4 this patient was observed throughout twelve episodes of coma or deep stupor

in which he was responsive only to painful stimuli. These episodes could be related to intolerance to more than 25 gm. of dietary protein ingested orally, to protein hydrolysate infusions or to oral administration of ammonium chloride. The sequence of the development of coma included the stages of flapping tremor of the outstretched extremities, usually associated with mental confusion, gradually increasing stupor (with the patient still responsive to stimuli) and coma. During recovery the sequence of events was reversed. His mental status, even when he was "alert," was markedly abnormal. This may have been related to the previous central-nervous-system syphilis.

On six occasions a temperature drop to below 97°F. was noted on the day before the onset of stupor. Also, during recovery from the stupor, he complained on several occasions of aching pain in the arms and legs without relation to local physical signs. The significance of these observations is not understood, but confirmation of the phenomenon of falling body temperature may make it a useful sign for predicting the onset of this type of coma.

Effect of Dietary Protein

Marked intolerance to dietary protein was observed in this man, and the speed of onset of stupor

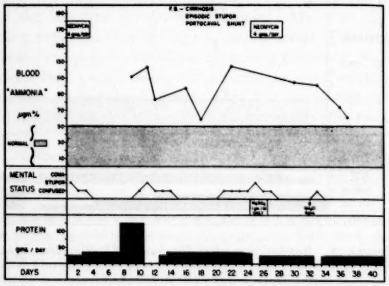

FIGURE 1. *Course during the First Forty Days in the Hospital.*

The mental state after ammonium chloride should show stupor instead of confusion. On various occasions it was necessary to administer fluids parenterally. Since this had no obvious effect on the course the details are not included. It was also necessary to administer various antibacterial agents in addition to neomycin for the febrile state that developed from time to time because of hypostatic pneumonia and urinary-tract infection.

was roughly proportional to the amount of protein ingested. Thus, 125 gm. of protein precipitated coma in three days whereas 35 gm. daily required nine days to produce deep stupor on one occasion and five days on another. So far as could be determined, approximately 25 gm. daily represented the maximum tolerable protein intake.

To evaluate the effects of certain kinds of protein an attempt was made to compare yogurt with meat as sources of protein. An additional reason for choosing yogurt was the possibility that this material would alter the intestinal flora. As shown in Figures 1 and 2 the patient tolerated a diet containing 25 gm. of protein without change in mental status. Subsequently, ingestion of 25 gm. of yogurt protein for five days, in addition to the 25-gm. protein diet, resulted in coma of twelve hours' duration. The 25 gm. of protein without supplement was then given for three days, after which a supplement of 25 gm. of protein from meat was begun. After two days of this diet coma occurred, lasting three days. Despite recovery

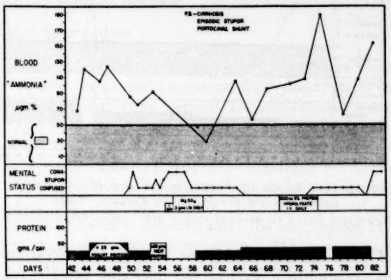

FIGURE 2. *Course during the Next Forty Days in the Hospital.*

of consciousness and reinstitution of the 25-gm. protein diet he remained confused for seven days. The blood ammonia was 121 microgm. per 100 ml. before the yogurt feeding and 92 microgm. before the meat ingestion. Despite the rapidity of onset and prolonged duration of disturbed sensorium that followed the meat regimen, in contrast to the effect of the yogurt feeding, we do not believe that any valid conclusions can be drawn from this single experiment since the patient had not completely recovered from the effects of the yogurt feeding when meat was introduced. Moreover, blood ammonia determinations were not carried out during the period of coma that followed the meat supplementation.

Effect of Protein Hydrolysate Intravenously

In a further attempt to augment this patient's protein intake, he was given 1000 ml. of a 5 per cent solution of protein hydrolysate* daily on two separate occasions. The first series of infusions was carried out during ingestion of a diet containing 35 gm. of protein, and after five days a period of confusion and drowsiness associated with a marked elevation in blood ammonia occurred (Fig. 2). Since stupor subsequently developed on the 35-gm. diet alone, the etiology of this episode was not clear. Accordingly,

*Available as Amigen from Mead, Johnson and Company, Evansville, Indiana.

when it had been established that he could tolerate this same diet without difficulty while receiving neomycin, the infusions were repeated. As shown in Figure 4 he became stuporous for several hours durthe infusion on the third day, responding only to strong stimuli. After this he reverted to his usual state. Again, on the fifth day, a similar episode of fifteen minutes' duration occurred during the infusion. Since the dietary intake was constant, as was the dosage of neomycin throughout this experiment, it is believed that these episodes of stupor were a direct result of the amino acid administration. In the first

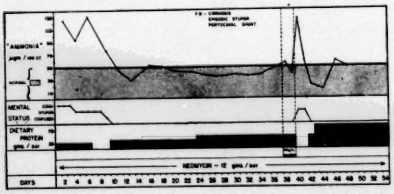

FIGURE 3. *Effect of Neomycin on the Blood Ammonia Levels despite the Increased Protein Intake. Neomycin failed to prevent stupor after ammonium chloride.*

of these episodes during the infusion the blood ammonia rose to a level of 135 microgm. per 100 ml.; no ammonia determinations were done during the second episode of stupor.

Since the gastrointestinal flora was presumably suppressed by the neomycin and the intravenous route of administration by-passed the gastrointestinal tract, the ammonia elevation was probably due to ammonia formation in another site or to ammonia release from the amino acid solution. Formation of ammonia by the kidney has been observed[8] and has been found to be increased by infusion of amino acids. Since this patient may not have had adequate hepatic extraction of ammonia such a renal mechanism may have precipitated the episodes of stupor.

Effect of Neomycin

Bacterial action upon urea and other nitrogenous compounds in the gastrointestinal tract is a probable mechanism for ammonia production. Therefore, attempts to eliminate or to alter the bacterial flora of the intestine by the use of antibiotic agents have been made. In the hands of others, however, such measures have not resulted in as clear-cut an effect upon both cerebral status and blood ammonia levels as we have observed. McDermott and Adams[4] were able to reduce the blood ammonia level in a patient with an Eck fistula with the use of sulfathalidine and a low-protein diet. Havens and Child[3] reported a case of cirrhosis with episodic stupor in which sulfaguanidine and later oxytetracycline were given simultaneously with a low-protein diet. Although the patient recovered they observed no clear-cut effects attributable to the antibiotic therapy alone. Silen et al.[9] administered a high-protein diet to dogs in conjunction with various antibacterial agents (neomycin, sulfasuxidine and tetracycline). Neomycin was the only agent that appreciably lowered the blood ammonia content in veins draining each of the sites tested: colon, small intestine and stomach, as well as the inferior vena cava. Mann and his associates,[10] working with dogs, indicated that oxytetracycline alone and oxytetracycline in conjunction with neomycin had no beneficial effect upon the blood ammonia level.

In view of the results obtained with neomycin by Silen and his colleagues we elected to use this agent in an attempt to reduce intestinal ammonia production in this patient. During the first eighty days of observation he received neomycin on two occasions as one of the therapeutic measures in episodes of coma. No marked effect upon the mental status could be attributed to this agent, but the dose used was only 4 gm. daily. After August 1, 1955, he received 12 gm. of neomycin daily almost continuously for eighty days. After initiation of neomycin the blood ammonia levels were consistently lower than those obtained before such therapy, and the majority were within normal limits (Fig. 3 and 4). Protein intake was progressively

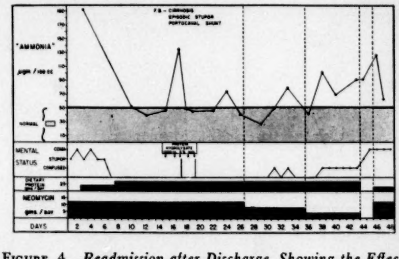

FIGURE 4. *Readmission after Discharge, Showing the Effect of Protein Hydrolysate Intravenously and of Decreasing Neomycin Dosage upon the Blood Ammonia.*

increased to as high as 90 gm. daily during this time, without untoward effect. Episodes of coma ensued, however, after discontinuance of the neomycin on two occasions: once during a discharge from the hospital and again in the hospital under observation. Diarrhea of varying severity was noted during the period of neomycin therapy, but for the majority of the time consisted of only 3 or 4 semisolid stools daily.

Since the dose of neomycin was chosen somewhat arbitrarily to provide a maximum effect a subsequent attempt was made to determine the smallest effective dose. Accordingly, with the dietary intake at a constant level of 35 gm. of protein, the antibiotic was withdrawn in a stepwise fashion (Fig. 4). Four days after neomycin was reduced to 8 gm. a day a flapping tremor was noted intermittently. Further reduction

to 4 gm. a day resulted in a persistent flapping tremor. In addition definite mental confusion was noted on one occasion. The onset of stupor coincided with the first day of complete cessation of neomycin; coma rapidly ensued.

Effect of Ammonium Chloride

This patient also showed marked intolerance to ammonium chloride given orally as demonstrated by the occurrence of coma after the administration of 6 gm. in a period of twelve hours. This occurred during ingestion of a 25-gm. protein diet, which he had previously tolerated (Fig. 1). Of some interest is the fact that neomycin did not protect him against the deleterious effect of ammonium chloride. Thus, the administration of 6 gm. daily for two days while he was receiving neomycin precipitated a sharp rise in blood ammonia after twenty-four hours to 128 microgm. per 100 ml. accompanied by stupor (Fig. 3). This observation suggests that neomycin offers protection against endogenous blood ammonia elevation by preventing ammonia formation, but does not prevent toxicity from exogenous ammonium salts.

Other Factors Influencing Ammonia

Since the large intestine may be a major site of ammonia production, attempts to cleanse this segment of the intestine should be beneficial. Mann et al.[10] have reported that in dogs a combination of fasting and enemas reduced blood ammonia concentrations. On several occasions in our patient, however, enemas yielded no beneficial effects. This may have been due to inadequate cleansing, since no strenuous effort was made to obtain flushing of the entire colon.

Numerous, previous authors[2,3,11-13] have failed to note a precise correlation between the clinical condition of the patient and the peripheral venous-blood ammonia level. We also observed no consistent correlation between the venous ammonia level and the clinical condition. On one occasion the patient was alert, with a blood ammonia of 124 microgm. per 100 ml., but on another occasion, forty-eight hours after the administration of ammonium chloride, he was still stuporous despite an ammonia level of 59 microgm. per 100 ml. (Fig. 3). In seven of the nine episodes of stupor or coma in which blood ammonia was measured, however, the ammonia level was above 100 microgm. per 100 ml.

This lack of precise correlation between blood ammonia and mental status may be related to the inability of our method and of most methods now in use to measure "true" blood ammonia as opposed to ammonia that is in part due to release from amino acids. On the other hand the lack of correlation may be due to the fact that most investigators, as well as ourselves, have been determining ammonia in venous blood. Bessman and Bradley[14] recently suggested that arterial ammonia levels correlate better with the clinical status and that venous determinations are altered by ammonia uptake in both peripheral and cerebral tissues. Studies in this laboratory have also demonstrated that arterial ammonia is higher than peripheral venous ammonia.[15] Further studies, however, will be necessary to determine the validity of arterial ammonia concentrations as a measure of cerebral dysfunction. The fact that we are determining extracellular ammonia concentration that may not necessarily reflect intracellular concentration may be partially responsible for the discrepancy. Unknown factors or biochemical mechanisms that are altered by changing blood ammonia concentrations may also be the mediators of abnormal cerebral function.

Other Observations

Flink et al.[16] have reported low serum magnesium levels after prolonged parenteral fluid therapy and in patients with delirium tremens. In both circumstances gross tremors were associated with the decreased magnesium levels, and symptomatic improvement followed the administration of magnesium sulfate intramuscularly. In several cirrhotic patients with flapping tremor and "impending coma" we have observed an apparent beneficial response after the intravenous administration of magnesium sulfate. Magnesium acts as a catalyst in the formation of adenosine triphosphate, which has been demonstrated as the energy source for the formation of glutamine from glutamic acid and ammonia. With this evidence an attempt was made to determine the effect of magnesium upon the state of consciousness in this patient's episodes of stupor. The administration of 1 or 2 gm. of magnesium sulfate intramuscularly daily on several occasions (Fig. 1 and 2), however, was without effect.

The fall in body temperature observed before and during the episodes of stupor or coma appears worthy of emphasis. The mechanism of this aberration is not clear, but it may be related to vasodilatation either owing to ammonia or a related circulating metabolic product or to transient dysfunction of the temperature-regulating center. Further observations seem necessary in view of the potential importance of this phenomenon in relation to the vascular dynamics of patients with advanced liver disease.

Summary

A case of episodic stupor following portacaval shunt in a patient with hepatic cirrhosis is reported.

No clear-cut correlation between the clinical condition and the venous-blood ammonia levels was observed.

The role of dietary protein as an etiologic factor in the pathogenesis of episodic stupor has been confirmed. In addition, the repeated administration of protein hydrolysate intravenously produced episodes of stupor.

Neomycin therapy resulted in marked reduction in blood ammonia levels and enabled this patient to ingest a regular hospital diet consisting of approximately 90 gm. of protein.

We are indebted to Misses Kathleen Collins and Mary Kearney for technical assistance and to Miss Marthana Hjortland for preparation and administration of the diets used.

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I^{131}-LABELED FAT IN THE STUDY OF INTESTINAL ABSORPTION*

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CHARACTERISTIC and reproducible curves of radioiodine blood levels have been demonstrated in normal persons after ingestion of an I^{131}-labeled test meal. This is true with the use of both radioactive tagged albumin[1] and radioactive tagged fat.[2] Furthermore, less than 2 per cent of radioactive material is recoverable in the total feces passed within forty-eight hours after ingestion of a fat test meal.[3] After normal controls were established, this method of study was applied to patients who had a variety of disorders of the gastrointestinal tract, to determine whether their radioactive blood levels and fecal content differed significantly from those found in normal persons.

Methods and Material

Test Meal

A cold emulsion and a "hot" emulsion were prepared for use in the laboratory. The cold emulsion consisted of 200 ml. of peanut oil, 200 ml. of water and 15 ml. of Tween 80. The "hot" emulsion consisted of 45 ml. of peanut oil, 5 ml. of I^{131}-labeled glycerol trioleate (2.0 millicuries of I^{131}), 50 ml. of water and 4 ml. of Tween 80. Each emulsion was prepared by mixing of the ingredients in a Waring blender for fifteen minutes. The I^{131}-labeled glycerol trioleate was obtained from Abbott Laboratories under authorization of the United States Atomic Energy Commission.

Each patient, in a fasting state, was given a test meal consisting of the following: that volume of "hot" emulsion which contained 25 microcuries of I^{131} to which was added sufficient cold emulsion to make a total of 1 ml. per kilogram of body weight. Twenty grams of barium sulfate was added to the test meal, and the entire contents mixed. The subject drank the test meal. The container was rinsed twice with 50 ml. of tepid water, which was likewise ingested. The container was assayed for residual radioiodine, which was taken into account in the final analysis. Twenty drops of Lugol's solution was given immediately after the test meal.

Two milliliters of venous blood was withdrawn at hourly intervals for six hours after ingestion of the test meal. Each sample was placed in a separate tube and assayed for radioiodine content in a scintillation crystal-well counter. The total blood volume was assumed to be 7.2 per cent of body weight. With the use of the measured radioactivity of the 2-ml.

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sample and the calculated total blood volume, the total blood level of radioiodine was determined and expressed as a percentage of the ingested material. From these data a curve was constructed giving the relation of instantaneous radioactive I^{131} blood levels to time after ingestion of the test meal.

All stools passed during the next forty-eight hours were collected in individual containers, care being taken to keep the samples free of urine. The containers used were plastic-lined, 0.5-liter, waterproof cartons (Sealright, Alservis containers).

Each container was individually assayed for radioiodine content with a scintillation crystal detector, which was positioned 15 cm. above the top surface of the container. The amount of radioiodine recovered in the feces was expressed as a percentage of the ingested material.

TABLE 1. *Classification of Patients.*

CLASSIFICATION		NO. OF PATIENTS
Functional gastrointestinal disturbances		44
Gastrointestinal diseases		57
Pancreatitis	18	
Carcinoma of pancreas	13	
Sprue	5	
Whipple's disease	2	
Regional enteritis	3	
Ulcerative colitis	8	
Cirrhosis of liver	8	
Previous gastric surgery for peptic ulcer		79
Partial resection	64	
Vagotomy with gastroenterostomy	15	
Total		180

One hundred and eighty patients were studied and for convenience were divided into three groups: functional disturbances; gastrointestinal diseases; and previous surgery for peptic ulcer (Table 1). Statistical analysis of the results was conducted as follows: the four-hour, five-hour and six-hour blood values were added in each case, and the mean value and standard deviation were determined for each group. A "t" test was performed on each group using the mean of the normal group as the true mean. The Table value of "t" having a probability of 0.01 was used for comparison. Thus, if a calculated value of "t" from one of the groups was rejected as being abnormal, there would be less than a 1 per cent probability of rejecting a normal group. To test the results in the individual patient, a 95 per cent confidence limit was established, the mean value of the sum of the four-hour, five-hour and six-hour blood levels of the normal group being used. The individual result was considered abnormal if it fell below the 95 per cent confidence limit, or if the radioiodine content of the stool exceeded 5 per cent.

RESULTS

Functional Disturbances

In 44 patients whose histories did not suggest organic disease and whose findings were entirely

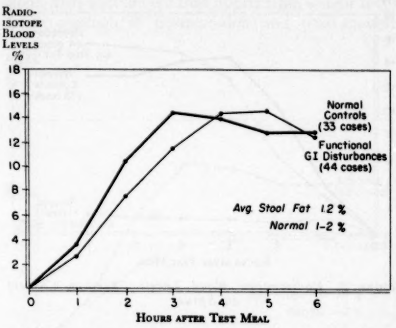

FIGURE 1. *Radioisotope Blood Levels (Average Curves) in Functional Gastrointestinal Disturbances.*

normal diagnoses of functional disturbances were made. The blood levels of every individual in this group were well within normal limits, as was the

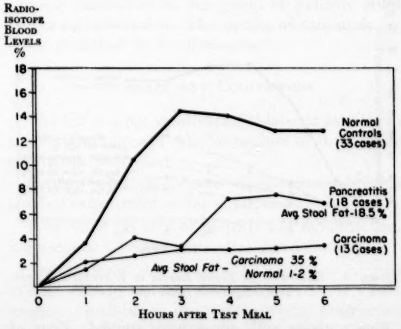

FIGURE 2. *Radioisotope Blood Levels (Average Curves) in Diseases of the Pancreas (Chronic Pancreatitis and Carcinoma).*

content of radioactive material in the stool. The average blood levels in this group closely approximated those of the normal controls (Fig. 1).

Gastrointestinal Diseases

Eighteen patients had chronic relapsing pancreatitis, the diagnosis having been confirmed in every case

by operation. Treated as a group, the average blood levels were significantly lower than normal, and the radioactive material in the stool was definitely elevated (Fig. 2). On analysis of the individual test, 13 of the 18 patients had abnormal findings.

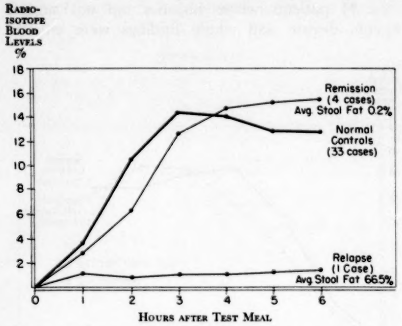
Radio-isotope Blood Levels %
Remission (4 cases) Avg. Stool Fat 02%
Normal Controls (33 cases)
Relapse (1 Case) Avg Stool Fat 665%
Hours after Test Meal

FIGURE 3. *Radioisotope Blood Levels (Average Curves) in Sprue.*

Thirteen patients had proved carcinoma of the pancreas. The blood levels in this group were markedly lowered, and the radioactive material in the stool greatly elevated in all but 1 patient (Fig. 2).

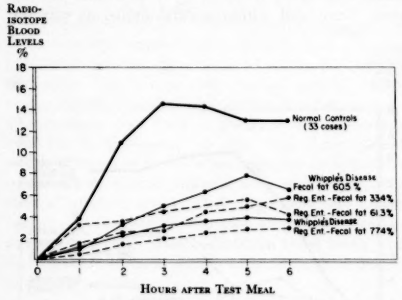
Radio-isotope Blood Levels %
Normal Controls (33 cases)
Whipple's Disease Fecal fat 605 %
Reg Ent - Fecal fat 334%
Reg Ent - Fecal fat 613%
Whipple's Disease
Reg Ent - Fecal fat 774%
Hours after Test Meal

FIGURE 4. *Radioisotope Blood Levels in Whipple's Disease and Regional Enteritis.*

Five patients with sprue were studied. Four of these were in clinical remission, and the radioactive values of the blood and stool were within normal limits in every case. The blood values of the patient in relapse were profoundly lowered, and the stool content of radioactive material markedly elevated (Fig. 3).

Two patients with Whipple's disease and 3 with regional enteritis had marked lowering of the blood values and elevation of the radioactive stool content in every case (Fig. 4).

Eight patients with ulcerative colitis and 8 with cirrhosis of the liver were studied. The average values of the blood and stool were well within normal limits in each case (Fig. 5).

Previous Surgery for Peptic Ulcer

Seventy-nine patients who had had surgery for peptic ulcer were studied. In each case the test was performed at least six months after the operation. Sixty-four of these had a partial resection, and 15 a vagotomy with gastroenterostomy. The average radioiodine blood values were significantly lowered, and those of the stool elevated in each group (Fig. 6 and 7). Statistical analysis of the individual cases revealed that 53 per cent of these patients had abnormal values.

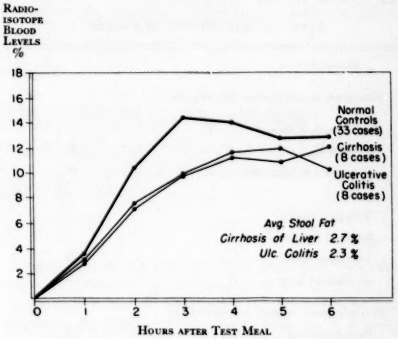

FIGURE 5. *Radioisotope Blood Levels (Average Curves) in Cirrhosis of the Liver and Ulcerative Colitis.*

Discussion

The need for a simple, accurate and reliable test of fat absorption from the gastrointestinal tract is readily apparent. The method employed in this study seems to offer an answer to this problem. The assumption that this test is actually a measure of fat absorption is supported by the following evidence: the radioactive material that appears initially in the blood cannot be dialyzed, indicating that I^{131} is attached to the fat as ingested or to a split product of digestion; electrophoresis of portal-vein blood in animals showed that the I^{131} is bound to beta-lipoprotein and the neutral fat fraction; the radioiodine blood levels after a test meal with I^{131}-labeled fat are profoundly lowered in pancreatectomized dogs, whereas after the ingestion of I^{131} alone, the blood levels are normal; a striking inverse relation exists between radioactive material in the blood and in the stool, a lowered blood level being invariably associated with an elevated fecal content and vice versa;

results of stool fat determinations are essentially the same with either fat-balance studies or radioactive technic; and the radioactive material that appears in the stool cannot be dialyzed, and on ether extraction was found in the fat fraction.[4]

On analysis of the data, there are several points that deserve emphasis. In the group of cases diagnosed as functional gastrointestinal disturbances, the blood levels and fecal excretion were all within normal limits. On the contrary, patients who had disease of the small bowel, regardless of cause, invariably had profound lowering of their blood levels and marked increase in radioactive content of the stool. Interestingly enough, the patients with sprue in clinical remission had completely normal blood and stool values, pointing to the reversibility of the pathologic process. Patients with disease of the colon only had normal absorption. This was also true of patients with cirrhosis of the liver.

The evidence in patients with disease of the pancreas points to faulty digestion rather than to intrinsic error of absorption. It is interesting that 12 of the 13 patients with carcinoma of the pancreas had abnormal levels. In each of these patients the

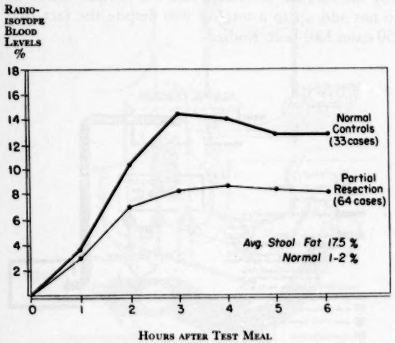

FIGURE 6. *Radioisotope Blood Levels (Average Curves) after Partial Resection for Benign Ulcer.*

tumor was located in the head of the pancreas, whereas in the patient whose findings were normal, the carcinoma was in the body and tail. The results in the group with pancreatitis were less consistent than those in patients with carcinoma. Possibly, this was due to the variable effect of the disease upon the external secretion of the pancreas. This study suggests that the test is of diagnostic value in patients suspected of having disease of the pancreas, especially carcinoma. Although normal values do not exclude pancreatic disease, an abnormal test is strongly suggestive of pancreatitis or carcinoma in the absence of small-bowel disease, pyloric obstruction or previous gastric surgery. It is quite obvious that the test does not distinguish between carcinoma and pancreatitis.

Analysis of the results in patients who have previously had gastric surgery for peptic ulcer points conclusively to impaired fat absorption in the majority of cases. Fifty-three per cent of all patients in this group had significant lowering of the blood curves and increase in radioactive content of the stool. It is well known that appreciable weight loss is fairly common in postresection and postvagotomy

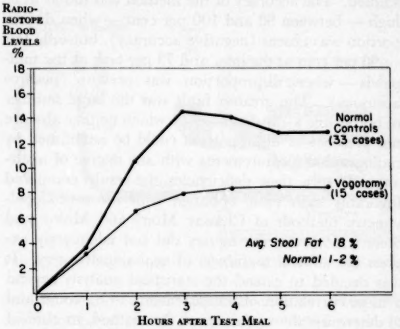

FIGURE 7. *Radioisotope Blood Levels (Average Curves) after Vagotomy and Gastroenterostomy for Benign Ulcer.*

patients. Our findings suggest that one of the factors causing weight loss in this group of patients is impaired fat absorption. The results of this study are being published in detail elsewhere.[5]

Summary and Conclusions

The use of a test meal with I^{131}-labeled fat offers a simple, accurate and reliable method of determining absorption of fat.

Patients with small-bowel disease invariably had marked impairment of fat absorption.

Fifty-three per cent of patients had significant impairment of fat absorption after gastric surgery.

An abnormal test is strongly suggestive of pancreatic disease, in the absence of previous gastric surgery, small-bowel disease or pyloric obstruction.

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INTEGRATION OF CEPHALOPELVIMETRY INTO AN OBSTETRIC WARD SERVICE*

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A STATISTICAL analysis of the correlation of x-ray cephalopelvimetry to obstetric outcome has just been completed. The records of 350 patients measured by the Ball method and delivered on the wards of the Sloane Hospital for Women were studied. The accuracy of the method was found to be high — between 98 and 100 per cent — when disproportion was absent (negative accuracy), but only fair — 90 per cent at the inlet and 73 per cent at the midpelvis — when disproportion was present (positive accuracy). The greatest fault was the large number of borderline x-ray diagnoses in which neither absence nor presence of disproportion could be established by radiographic measurements with any degree of assurance. Despite these deficiencies, the results compared favorably with those obtained with the cephalopelvimetry methods of Chassar Moir[1] and Moloy and Steer.[2] However, the figures did not adequately express the *clinical usefulness* of cephalopelvimetry. It was decided to extend the statistical analysis beyond a mere correlation of measurements to outcome and to determine the *usefulness* of the method, its clinical ramifications and its integration into an obstetric ward service.

METHOD OF ANALYSIS

All x-ray diagnoses were classified according to the difference between the size of the fetal head and the size of the maternal pelvis, as follows:

"A" = no radiologic disproportion.

"B" = radiologic borderline disproportion.

"C" = high radiologic disproportion.

The exact definition of each term has been established by statistical means.[3] When possible, cases were labeled by one of these terms. The results were entered on "flow charts" (Fig. 1-3), and for clarity the figures were rounded to the nearest multiple of 5, with the following exceptions:

Figures over 100 were rounded to the nearest multiple of 10, and figures over 1000 to the nearest multiple of 100.

Figures under 20 and larger figures of exceptional importance were given accurately.

By such means, percentage figures likely to be calculated from the charts are correct within 0.5 per cent.

The width of the channels was drawn in proportion to the number of patients they represented except the one for the 2300 patients entering the ward service, which had to be condensed for economy of space. The channels were shaded according to the diagnosis or the outcome. White channels indicated a diagnosis of "no disproportion" or the event of a normal delivery. Black channels symbolized a diagnosis of "high radiologic disproportion" or the event of a surgical delivery. A surgical delivery was either a cesarean section or a mid-forceps delivery. The hatched channels represented an undecided diagnosis.

FINDINGS

Figure 1 presents an over-all description of the events that took place. Twenty-six surgical deliveries for reasons *other* than cephalopelvic disproportion have been omitted from this graph. This explains why the surgical deliveries and the normal deliveries do not add up to a total of 350 despite the fact that 350 cases had been studied.

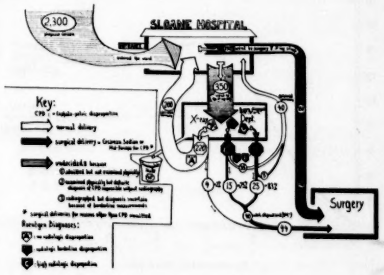

FIGURE 1. *Diagnoses and Outcome in 2300 Cases.*

When the flow of patients shown in Figure 1 is followed, it is noticed that of the 2300 pregnant women entering the Sloane Hospital for delivery only 350 were sent to the x-ray department for cephalopelvimetry. One hundred and fifty patients had a surgical delivery without having an x-ray examination. This group contained among others all but 3 of the repeat sections performed in the entire patient material. (Figure 3 gives a more detailed analysis of this group.)

Of the 350 cases examined in the x-ray department, 220 were diagnosed as "A" on the basis of x-ray measurements. Of these only 4 (less than 2 per cent) required surgical intervention for cephalopelvic dis-

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proportion. Evidently, an x-ray diagnosis of "no radiologic disproportion" is very reliable. Thirty were diagnosed as "C" and considered to represent "high radiologic disproportion." In this group 25, or 83 per cent, required surgical delivery for disproportion. Sixty were diagnosed as radiologic borderline disproportion ("B"). Fifteen of these (25 per cent) required surgical delivery for disproportion.

These findings make it obvious that the number of radiologic borderline diagnoses is too large. This has since been ameliorated by technical improvements. A precise method for measuring the interspinous diameter named orthometric view[4] was adopted. The fitting of a circle into an actual-size scale drawing of the mid-pelvis has reduced the number of borderline diagnoses further. Nevertheless, the large number of radiologic borderline diagnoses has remained

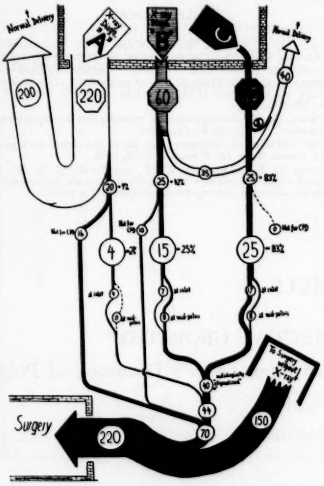

FIGURE 2. *Outcome According to Presence or Absence and Type of Disproportion.*

a major problem in the evaluation of the mid-pelvis. In the material here presented, 35 of the 60 cases diagnosed as "B" according to x-ray measurements resulted in normal deliveries. If one combines this group "B" with the group "C" by considering each case of either group as "radiologically stigmatized," one obtains 40 surgical deliveries for disproportion and 40 normal deliveries. In short, for a radiologically stigmatized case (that is, one in which x-ray measurements raise the suspicion of or clearly indicate the presence of disproportion), the chances for a surgical delivery or for a normal delivery are exactly even.

In 40 patients the measurements or the follow-up studies were incomplete. There is nothing to indicate that any of these studies led to an incorrect x-ray diagnosis. In the majority of these, the ischial spines could not be identified. In a few breech presentations the fetal head was only partially included on the films and could not be measured, being only estimated as small or large. General inspection of films in either category indicated presence or absence of disproportion and provided enough information to dispense with additional x-ray films. These studies were therefore

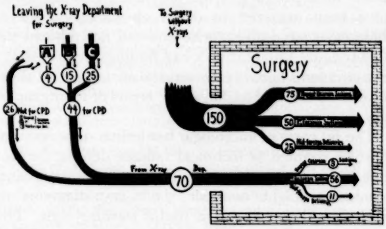

FIGURE 3. *Detailed Analysis of Cases Charted in Figure 1.*

neither diagnostic nor technical failures. However the incompleteness of their measurements made it impossible to assign these cases a diagnostic roentgenometric classification of "A", "B" or "C".

DETAILED ANALYSIS

A more detailed analysis is shown in Figure 2. Here, the outcome in all cases diagnosed roentgenometrically is shown. In the cases classified as "A", 16 patients underwent surgical delivery for reasons *other* than disproportion. Of interest is the fact that all 4 possessing disproportion in this group required cesarean section at the *inlet,* and none at the mid-pelvis.

In Class "B", 10 surgical deliveries for reasons other than disproportion occurred. Surgical deliveries for disproportion were divided about evenly between inlet and mid-pelvis in this class.

In Class "C", *all* surgical deliveries were performed because of cephalopelvic disproportion. Seventeen of these occurred at the inlet, and 8 at the mid-pelvis.

No distinction is made in Figures 1 and 2 between cesarean section at the mid-pelvis and mid-forceps delivery because only 2 mid-forceps deliveries for cephalopelvic disproportion occurred — 1 in Group "B" and the other in Group "C". Nine other records of mid-forceps deliveries were reviewed. They were found, when critically assessed, to have been performed for reasons other than disproportion. The ratio of 2 mid-forceps deliveries to 14 mid-pelvic cesarean sections performed for disproportion reflects a trend in the practice of obstetrics that established

itself in the past two decades. Cesarean section at the mid-pelvis is considerably less traumatic to the fetus than mid-forceps delivery. The routine availability of blood transfusions and the advent of antibiotics have made cesarean section much safer to the mother and removed almost all objections to this procedure. It has become the preferred method in the management of mid-pelvic disproportion.

Discussion

Figures 1-3 indicate that in 9 patients the measurements were contrary to the obstetric outcome. These have been analyzed in detail elsewhere.[5] Four of these cases were no surprise and did not mislead the obstetrician. Qualitative x-ray findings overruled the measurements here. However, statistically, all of them have to be counted as diagnostic errors of roentgenometry.

The 60 cases of radiologic borderline disproportion must be counted as technical failures despite the fact that obstetricians favorably inclined toward roentgenometry might consider the x-ray diagnosis of borderline disproportion a useful warning sign. The fact remains that in 69 cases roentgenometry failed because it provided either an indefinite or an incorrect answer.

One can conclude that cephalopelvimetry is useful because it proved capable of reducing the number of doubtful cases from 350 to 69, or to approximately a fifth. The x-ray department may act as a filter here. After most doubtful cases have passed through it, a few unresolved cases remain. Only in 5 (1.4 per cent) patients was the procedure misleading. This is not too serious a fault because the obstetrician does not rely on x-ray measurements alone.

Roentgen cephalopelvimetry was used sparingly in this series. Only when a reasonable clinical doubt of the presence or absence of disproportion existed was the procedure requested. In institutions in which it is used more liberally or routinely, the number of normal cases among those examined radiographically will be much larger. Since x-ray cephalopelvimetry is most accurate and definite in normal cases, the percentage of failures will be considerably less. In short, the method has been given the most severe test likely to be encountered in obstetric practice.

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SPECIAL ARTICLE

EXTREME POLYURIA IN OBSTRUCTIVE UROPATHY*

Report of a Case of "Water-Losing Nephritis" in an Infant, with a Discussion of Polyuria

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In 1954 Roussak and Oleesky[1] described 2 patients with renal disease who exhibited a syndrome simulating diabetes insipidus, which the authors called "water-losing nephritis." One of these patients had multiple myeloma; the other had carcinoma of the prostate with secondary hydroureters and hydronephrosis. Before the onset of azotemia, albuminuria or other signs of renal insufficiency, both patients exhibited striking polydipsia, polyuria and hyposthenuria‡ that were unresponsive to thirst or to exogenous vasopressin. Neither gave a history or diagnostic evidence of any extrarenal disease that might account for the polyuria. The patient with myelomatosis eventually died in renal failure, but, after prostatectomy and relief of urinary obstruction, the patient with carcinoma of the prostate recovered from his polyuria and was able to produce a concentrated urine in response to thirst and the administration of vasopressin.

The following case of an infant with an obstructive uropathy with many similarities to the cases of Roussak and Oleesky was investigated along similar lines.

*Student essay (first prize) from the University of North Carolina School of Medicine.

From the Department of Pediatrics, University of North Carolina School of Medicine, and the Pediatric Service, North Carolina Memorial Hospital.

The work on which this paper was based was carried out during the course of a clinical clerkship in pediatrics.

†Intern, Second (Harvard) Medical Service, Boston City Hospital, Boston; formerly, fourth-year student, University of North Carolina School of Medicine.

‡Hyposthenuria as used throughout this article refers to urine with an osmolar concentration lower than that of plasma or to urine with specific gravities consistently below 1.010.

Case Report

E.B. (N.C.M.H. 02-84-33), a 6-month-old Negro male infant, was admitted to the Pediatric Service of the North Carolina Memorial Hospital on March 16, 1955, for evaluation of a persistent urinary-tract infection. The patient was born after an uncomplicated full-term pregnancy and weighed 3.5 kg. (7 pounds, 13 ounces) at birth. On breast milk and multivitamin supplements he apparently thrived and gained weight normally. At the age of 7 weeks he was hospitalized after the onset of fever, pyuria, mild diarrhea and a brief convulsive seizure. At this time he exhibited an erratic febrile course, with temperatures as high as 105°F. After 5 days of treatment with several chemotherapeutic agents he was discharged somewhat improved.

After this episode, he was changed from breast feeding to an evaporated-milk formula supplemented by juices and vitamins; however, in spite of an adequate intake he lost 1.3 kg. (3 pounds) during the next 3 months. At the age of 4 months the mother noticed the sudden onset of increased urinary frequency, which reached such proportions as to require diaper changes as often as 2 to 4 times every hour. There was a concomitant onset of thirst, evidenced by an average daily fluid intake of 1050 to 1350 ml. (35 to 45 ounces) of water in addition to 960 ml. (32 ounces) of formula.

At the age of 5 months the patient was again noted to have pyuria and cylindruria. At this time treatment with a sulfonamide was started, but the pyuria persisted, as did the polyuria and polydipsia. Three weeks before admission, he began to receive injections of desoxycorticosterone acetate in

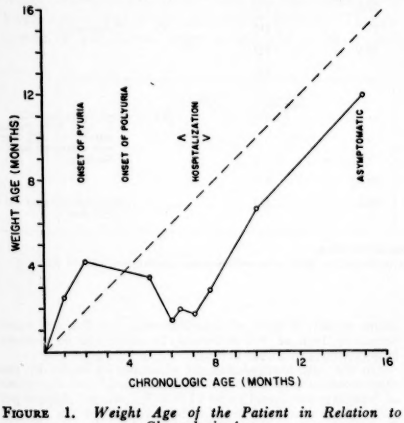

Figure 1. *Weight Age of the Patient in Relation to Chronologic Age.*

The values indicated were taken from the Stuart growth chart for infant boys.[7]

oil, 5 mg. daily; these were continued until admission. The polyuria and polydipsia persisted, and several changes in antibiotic therapy produced no improvement in the urinary findings. He was therefore admitted to this hospital for further study.

The remainder of the history was unremarkable. Careful questioning revealed no family history of polyuria, polydipsia or renal disease.

Physical examination revealed a small, irritable infant 62 cm. (24½ inches) tall and weighing 5.2 kg. (11 pounds, 5½ ounces) — both these measurements were below the 3d percentile (see Fig. 1 for weight age). The abdomen was distended, and the urinary bladder was thought to be palpable just below the umbilicus. Enlarged renal masses were felt bilaterally. The foreskin of the penis was easily retractable, and there was no meatal stenosis. Rectal examination revealed only the distended urinary bladder. The remainder of the examination was within normal limits.

The temperature was 98.6°F. by rectum, and the blood pressure 110/50.

Examination of the blood showed a hemoglobin of 9.5 gm. per 100 ml. and a white-cell count of 19,000, with 51 per cent neutrophils, 47 per cent lymphocytes and 2 per cent eosinophils. A sickle-cell preparation and serologic tests for syphilis were negative. The initial urinalysis showed a specific gravity of 1.003, no reducing substance or ketones, a trace of protein and a centrifuged sediment consisting of numerous white blood cells, rare red blood cells and many bacteria. Cultures of the urine revealed a mixed flora composed of the klebsiella–aerobacter group and beta-hemolytic enterococci. Sensitivity studies showed these organisms to be resistant to a wide variety of therapeutic agents.

Despite a copious flow of urine the bladder remained distended until free drainage was established by an indwelling catheter. The patient was started on sulfisoxazole, chloramphenicol and nitrofurantoin. A cystogram and urethrogram on the 2d hospital day demonstrated dilatation and trabeculation of the bladder, with evidence of obstruction at the bladder neck. Cystoscopy on the 7th hospital day showed hypertrophied musculature of the bladder neck, with encroachment on the internal urethral orifice.

On the 12th hospital day a suprapubic cystotomy was performed, and the internal urethral orifice was found partially occluded by hypertrophic tissue at the vesical neck. A wedge resection of this tissue established free drainage. Histologically, the resected tissue showed dense fibromuscular connective tissue with chronic inflammation.

Cultures of the urine continued to grow klebsiella-aerobacter organisms, and on the 17th hospital day therapy was changed to tetracycline and polymyxin B because of slight sensitivity of the organisms to these agents. However, the urine remained infected throughout the hospital stay.

The daily intake of fluid and output of urine were much higher than would be expected for an infant weighing 5 kg. (11 pounds), the average daily intake being 1900 ml. and the average urinary volume 1400 ml. (reported volumes were often minimal because of failures in accurate collection and losses through the suprapubic wound). The determinations of the specific gravity ranged from 1.001 to 1.005, except for 1 isolated measurement, which was 1.012. The reaction of the urine with nitrazine paper was consistently acid; a trace of protein was usually found, and reducing substances and ketones were never present. The centrifuged sediment invariably contained large numbers of white blood cells and bacteria, but only an occasional red blood cell.

The white-cell count ranged from 37,000 early in the hospital course to 12,000 at the time of discharge. Anemia was also present and was treated with transfusions of whole blood. The patient exhibited an erratic febrile course, the temperature ranging from 96.4° to 104.6°F., and there were daily fluctuations of weight as great as 0.5 kg. (1 pound).

At discharge after 42 days in the hospital he was alert and happy. Although he was afebrile, the urine was still infected, and the abnormally high daily intake of fluid and output of urine were unchanged. He was discharged on treatment with sulfisoxazole, and his mother was instructed to maintain a high intake of liquids.

He was not seen again in this clinic. However, he was followed by his family physician, who reported that at 10 months of age he was thriving and weighed 7.3 kg. (16 pounds) — 3d percentile (Fig. 1). At 14 months of age he no longer exhibited polyuria and polydipsia, and laboratory studies showed a hemoglobin concentration of 11.8 gm. per 100 ml. and white-cell count of 8600. Urinalysis at the age of 15 months was reported as showing no reducing substance or ketones, no protein and no formed elements; the quantity was insufficient for a determination of specific gravity. The weight at this time was 9.8 kg. (21 pounds, 11 ounces) — 25th percentile (Fig. 1). Unfortunately, it was not possible to do further follow-up studies.

The chemical analyses of serum performed in the hospital are shown in Table 1. On admission the patient exhibited marked hyperchloremia and depression of the serum carbon dioxide content, which were interpreted as being due to a hyperchloremic acidosis. There were also moderate eleva-

tions of the urea nitrogen and phosphate levels in the serum. Within 6 days of catheterization and the establishment of free drainage of urine from the bladder, the level of urea nitrogen in the serum had fallen to a normal value, and the hyperchloremia was somewhat ameliorated. After that time, elevated levels of urea nitrogen were noted only during periods of clinical dehydration and hypernatremia. During states of adequate hydration the levels of calcium and phosphorus were normal for this age (11.3 mg. and 5.8 mg. per 100 ml., respectively), and the only detectable abnormality was the mild hyperchloremic acidosis. Two determinations of venous-blood pH were 7.30 and 7.31, and the pH of a number of freshly voided specimens of urine varied from 6.3 to 6.9 (these pH determinations were made with the glass electrode at 37°C.). The alkaline phosphatase was 10 Bodansky units.

osmolarity of the urine (determined by the Fiske osmometer) never approached that of the plasma, and it was evident that the patient was unable to produce a concentrated urine under the stimulus for endogenous antidiuretic-hormone production or with exogenous vasopressin. The results of this study clearly indicated that there was an unresponsiveness of the renal tubules to the antidiuretic hormone, and that neither primary polydipsia nor supraopticoneurohypophyseal disease could be a single cause for the polyuria.

On the 28th hospital day, when the patient was clinically dehydrated and showed hypernatremia, it was decided to determine his response to repeated administration of vasopressin. The results of this study are summarized in Table 2. For 42 hours accurate measurements of intake and output were made, and during this time he received subcutaneous injections of vasopressin every 6 hours. Throughout the

TABLE 1. *Blood Chemical Studies.**

Hospital Day	Urea Nitrogen	Sodium	Potassium	Carbon Dioxide Content	Chloride	Whole Blood pH	Remarks
	mg./100 ml.	*milliequiv./liter*	*milliequiv./liter*	*millimols/liter*	*milliequiv./liter*		
1	33	137	5.4	12.4	116		Admission
3	23	147	4.4	12.7	122		Indwelling catheter inserted on 2d day and continued until 17th day
5	22						
8	16	133	4.4	20.0	98.4		2 days postoperative
14	14	147	4.6	22.5	112		
19	18	145	5.1	21.2†	119	7.30†	Dehydrated‡
28§	31	162	4.9	18.8	124		
29§	22	152			117		
30§	17	138					
35	14	147	4.5	21.5†	115	7.31†	Low solute formula & high fluid intake started on 32d day and continued until discharge
38	8	143	4.5	20.1	110		
41	14	142	4.9	21.6	113		Patient discharged on 42d day

*All determinations except pH performed on serum in duplicate using standard methods.
†Carbon dioxide content and pH (glass electrode at 37°C.) determinations performed on same venous-blood sample withdrawn without stasis.
‡Fluid intake during previous 12 hr. only 360 ml. (see text).
§Period of repeated administration of vasopressin (see Table 2).

On the morning of the 28th hospital day the patient appeared dehydrated. At this time the serum sodium was 162 milliequiv., and the chloride 124 milliequiv. per liter; the urea nitrogen was 31 mg., and the phosphorus 7.2 mg. per 100 ml. A review of the record revealed that the intake of fluid during the previous 12 hours had been only 360 ml. During the next 4 hours he received 410 ml. of fluid, and voided 270 ml. of urine with a specific gravity of 1.003 and a sodium concentration of 6.6 milliequiv. per liter. At the end of this time the serum sodium had fallen to 153 milliequiv. per liter. These findings indicated that under the stress of dehydration he was unable to conserve water normally, and that this loss of water was not the result of sodium diuresis.

Further study of the polyuria was undertaken by a technic similar to that described by Hickey and Hare[3]; the results are shown in Figure 2. The patient was maintained in a positive water balance, and the urine was accurately collected through an indwelling catheter. The rapid infusion of hypertonic saline solution (0.25 ml. per kilogram of body weight per min. of 2.5 per cent sodium chloride for 40 minutes) produced no prompt antidiuresis, and likewise intravenous administration of vasopressin only slightly decreased the flow of urine.* Throughout the procedure the entire period, in spite of hypernatremia and doses of vasopressin as high as 400 milliunits, he continued to produce large volumes of dilute urine.

*Parke, Davis Pitressin lot No. 189750 was used throughout the study of this patient and was biologically active in adult human subjects.

On the 31st hospital day the clearance of inulin by the continuous-infusion technic was determined,[3] and the mean of 5 periods was found to be 41.0 ± 4.0 ml. per minute per 1.73 square meters of body surface (about 34 per cent of the expected normal). After this procedure the excretion of phenolsulfonphthalein was found to be 48 per cent in 2 hours. Special care was taken to assure adequate hydration during both these procedures.

Total urinary amino acid excretions were measured on 5 24-hour specimens. Determinations by the method of Folin[4] ranged from 16 to 36 mg. of amino acid nitrogen per 24 hours.

Discussion

This patient exhibited a polyuria characterized by a copious flow of very dilute urine that was unresponsive to biologically active vasopressin. Polyuria that is not inhibited by antidiuretic hormone may occur as a symptom in a variety of diseases. In some cases this resistance seems to be a true defect

in renal responsiveness to the hormone, whereas in others it is only an apparent unresponsiveness. The more common examples of both these types are discussed briefly to delineate more clearly the nature of the polyuria present in this patient.

Mechanisms

An evaluation of polyuria necessitates some understanding of the physiology of water reabsorption by the kidney. According to a current hypothesis[5-7] water filtered by the glomerulus is reabsorbed at three different sites and by three different mechanisms during the formation of the final urine. It is thought that about 80 per cent of the filtered water is reabsorbed passively in the proximal tubule in isosmotic proportions incident to the active reabsorption of solutes. Upon reaching the distal tubular segment, water is again reabsorbed isosmotically by a mechanism dependent upon the presence of antidiuretic hormone and the reabsorption of solutes (T^DH_2O). A third and still more distal site of water reabsorption removes solute-free water (T^CH_2O) from the tubular urine. By the operation of this final mechanism of water reabsorption, urine may be concentrated to levels above that of the glomerular filtrate. This removal of solute-free water is thought to be limited

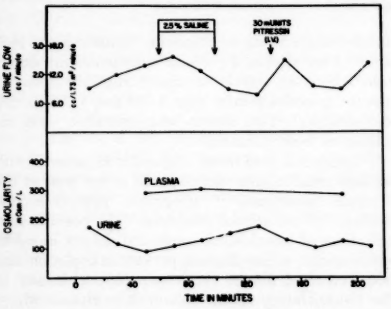

FIGURE 2. *Results of the Hickey–Hare Procedure.*[3]

during high rates of urine flow by a maximal rate of reabsorption about (5 to 7 ml. per 1.73 square meters of body surface per minute),[8] and during low rates of urine flow by a maximal concentration of osmotically active solutes (about 1200 to 1400 milliosmols per liter).[8] In terms of this concept hyposthenuria is achieved by the failure of water to follow solute reabsorption in the distal tubular segment because of the absence of, or lack of response to, antidiuretic hormone.

Osmotic Diuresis

When solutes that cannot be reabsorbed by the tubule are present in the glomerular filtrate or are present in amounts that exceed the tubular capacity for reabsorption, an osmotic (solute) diuresis ensues.[8] In this situation at high rates of solute excretion, there may be an apparent end-organ unresponsiveness to antidiuretic hormone, in that vasopressin or hydropenia or both do not appreciably affect either the rate of flow or the concentration of the urine. In terms of the hypothesis discussed above, maximal activity of antidiuretic hormone results in tubular urine that is isosmotic with the glomerular filtrate before the distal removal of solute-free water. The presence of large amounts of unreabsorbed solutes will therefore cause the distal mechanism to be presented with a large isosmotic volume, and since this mechanism is limited in rate, maximal concentration cannot be achieved. The greater the solute load, the greater the isosmotic volume reaching the limited distal mechanism will be; hence, the greater the urine flow will be and the closer the osmolarity will approach that of the glomerular filtrate.[8]

It has been suggested that the polyuria of chronic renal failure may be due to an osmotic diuresis. With a great loss of functioning nephrons, the remaining units may be filtering at a much greater than normal individual rate, and this together with an elevated urea nitrogen level would result in an abnormally high rate of solute excretion and a consequent "osmotic diuresis" for each individual nephron.[9] The resulting polyuria is associated with urines whose osmolar concentrations are fixed near that of the glomerular filtrate, and the loss of water in this condition is obligatory to the excretion of solutes.

Apparently, an osmotic diuresis is also responsible for the polyuria seen during the recovery phase of acute tubular necrosis. This may be due to an inability of the damaged tubules to reabsorb solutes, to elevated levels of blood urea, to specific defects in water reabsorption or to a combination of these factors.[10] Uncontrolled diabetes mellitus with extreme degrees of glycosuria is another common condition resulting in osmotic diuresis, and here the loading solute is glucose, which is filtered in amounts that exceed the tubular capacity for reabsorption.[8]

Water Diuresis

In this situation there are large volumes of urine with osmolar concentrations lower than that of the glomerular filtrate. In accordance with the theory discussed, dilute urine (hyposthenuria) can only be produced by some lack of action of antidiuretic hormone. In the absence of this substance, water that reaches the distal tubular segment is not reabsorbed along with solute, and a large hypotonic volume reaches the more distal site (T^CH_2O). The volume and concentration may then be altered by the amount of solute-free water reabsorbed (5 to 7 ml. per 1.73 square meters of body surface per minute), but this is usually insufficient to produce a concentrated

urine. Hence, an inability of the renal tubule to respond to antidiuretic hormone would result in hyposthenuria.

Nephrogenic diabetes insipidus is an inherited disorder in which an inability of the renal tubules to respond to antidiuretic hormone is thought to exist. The genetics involved in the transmission of this disease are not clear, and although it does appear in females,[11-13] it more commonly affects males.[11-17] The disease is characterized by an onset shortly after birth and a persistence throughout life.[14] During infancy it is manifested by erratic and unexplained fever, constipation, vomiting, polydipsia and polyuria, rapid dehydration and hypernatremia and the inability to excrete a concentrated urine.[16] The hyposthenuria seen in this disease is refractory to hydropenia or to vasopressin.[11-17] Most reports suggest that in the absence of dehydration, the concentrations of sodium, chloride and urea nitrogen in the serum[13,15,17] are normal, as are certain discrete tests of renal function, including mannitol [11,14,16] and inulin clearance,[17] effective renal plasma flow[11,14,16] and phenolsulfonphthalein excretion.[11,12] However, some abnormalities of renal function have been noted, but sufficient data have not been reported to allow any final conclusions. Histologic studies of the kidney in 2 cases revealed only nonspecific changes in the proximal tubules.[17,18]

Dancis and his co-workers[11] were able to demonstrate antidiuretic substance in the urine of their patient with nephrogenic diabetes insipidus, and Williams and Henry[14] were unable to demonstrate inactivation of vasopressin by the blood of a patient with the disease. The latter authors postulated a congenital defect in the loop of Henle and in the distal convoluted tubule. Cannon[13] recently reported studies of 2 patients with "hereditary extra-pituitary diabetes insipidus," and his findings, if confirmed, would make it unlikely that an end-organ resistance is the single responsible factor in this disease.

III Defined Polyurias

There are certain other conditions in which polyuria is a prominent symptom but in which the mechanisms involved are not clear. Large volumes of urine have been frequently noted in patients in association with a variety of hypercalcemic states,[1] and Albright and Reifenstein[19] have described a patient with hyperparathyroidism who was unable to produce a concentrated urine in response to vasopressin.

Potassium depletion seems to interfere with the urine-concentrating mechanisms. Schwartz and Relman[20] have studied 2 patients with potassium depletion who were unable to concentrate the urine to specific gravities greater than 1.013 and 1.005 during dehydration. This defect was reversible with repletion of body potassium.

Polyuria has been noted frequently in patients with various renal tubular defects, such as are seen in the Fanconi syndrome,[21,22] idiopathic hyperchloremic acidosis[23,24] and related disorders. The possible contributions of coincidental congenital defects in water reabsorption, solute diuresis, potassium depletion and acquired renal disease (such as nephrocalcinosis) to the concentrating defects remain to be elucidated.

Hyposthenuria has been reported in association with the hypertension of unilateral renal disease.[25,26] Deming[25] has studied such a patient and concluded that the dilute urine was a product of both the uninvolved and the diseased kidneys. The concentrating defect in this patient was not affected by thirsting, but was reversible after nephrectomy and the return to the normotensive state.

TABLE 2. *Summary of Period of Repeated Vasopressin Administration.*

PERIOD	DURATION OF PERIOD	DOSE*	INTAKE	URINARY VOLUME	SPECIFIC GRAVITY†	SERUM SODIUM‡	SERUM UREA NITROGEN‡	BODY WEIGHT
	hr.	*milliunits*	*ml.*	*ml.*		*milliequiv./liter*	*mg./100 ml.*	
1	4	—	410	270	1.003	161	31	4.8 kg. (10 lb. 12½ oz.)
2	6	40	480	260	1.002	153	30	
3	6	40	405	400	1.003			
4	6	40	305	300	1.003			
5	6	40	205	270	1.003			
6	6	400	610	270	1.003	152	22	
7	6	400	610	450	1.004			
8	6	400	415	425	1.004	138	17	5.3 kg. (11 lb. 11⅔ oz.)

*Pitressin in aqueous solution administered subcutaneouly.
†All determinations of specific gravity in study of this patient by standard clinical urinometer.
‡All serum determinations performed at beginning of each period, except final ones, which represent end of last period.

Comment

In the case presented above, obstruction of the lower urinary tract resulted in hydroureters, hydronephrosis, chronic infection and impairment of renal function measurable in terms of a hyperchloremic acidosis, a retention of phenolsulfonphthalein, a decreased clearance of inulin and a defect in the reab-

sorption of water. The presence of high flows of very dilute urine and the failure of vasopressin either to reduce the flow appreciably or to increase the concentration to plasma levels suggest an inability of the renal tubule to respond to antidiuretic hormone.

The very dilute character of the urine was not consistent with that of an osmotic diuresis. Furthermore, there was no evidence of hypercalcemia, potassium depletion or unilateral renal hypertension. Aminoaciduria and glycosuria were not present and hence make the Fanconi syndrome unlikely. Although the patient had a hyperchloremic acidosis, the association of this finding with the obvious obstructive uropathy and its amelioration after corrective surgery suggests that the acidosis had its origin in the acquired renal disease rather than as a coincidental congenital defect.

Some of the symptomatology displayed by this infant as well as the results of the physiologic studies are similar to those seen in nephrogenic diabetes insipidus. However, the appearance of signs of renal diseases before the onset of polyuria, the lack of a family history and the apparent later recovery of the patient all suggest that the urinary-concentrating defect was acquired as a part of the more basic renal disease.

Thus, it appears that this case represents another example of the acquired renal lesion that Roussak and Oleesky[1] have called "water-losing nephritis." It is interesting that both this patient and 1 of those previously described had obstructive lesions that were functionally analogous, and that both patients recovered after the relief of this obstruction. The importance of obstruction of the lower urinary tract in the production of this syndrome is only speculative; however, in view of the references[27,28] in the literature to the not infrequent association of polyuria with such obstructions, this syndrome, perhaps in varying degree, may be more prevalent than is realized.

The term "water-losing nephritis"[1] was suggested to emphasize the degree and the mechanism of the polyuria occurring in this syndrome. However, it may be misleading in that it diverts attention from the significant though less marked degree of polyuria occurring in chronic renal failure secondary to solute excretion.

Summary

A case of a six-month-old infant with striking polyuria secondary to obstructive uropathy and renal disease is presented. Investigation of the polyuria revealed a persistent hyposthenuria unresponsive to thirst and vasopressin. The mechanisms producing polyuria in a variety of clinical states are briefly discussed, and evidence delineating these from that occurring in the case reported is presented.

It is concluded that this case represents an acquired, reversible renal tubular unresponsiveness to the antidiuretic hormone.

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MEDICAL PROGRESS

DISEASES OF MEDICAL PROGRESS*

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THE history of medicine is replete with examples of illness resulting from sound therapeutic endeavor. The emergence of a new syndrome while the patient is being treated for another condition has long been recognized in clinical medicine. However, in recent years the development of potent new therapeutic agents, improved surgical procedure and more efficient equipment has forced this facet of medicine into unprecedented prominence.

This phenomenon may arise from a variety of causes. In the past, emphasis was placed on such things as product impurity, acute or chronic overdosage and ill defined individual sensitivity. In the diseases that are the subject of this paper, the mechanism frequently evades explanation. Biochemical, enzymatic and metabolic lesions have been suspected. Idiosyncrasy and hypersensitivity reactions have come under consideration.

In any event, the common denominator may be defined as "diseases that would not have occurred if sound therapeutic procedure had not been employed." This is an oblique approach, but as such reveals the problem from a new aspect — that is, "diseases of medical progress."

COLLAGEN AND COLLAGENLIKE DISEASES

Periarteritis Nodosa[1-7]

The rising incidence of periarteritis nodosa since 1936 (when sulfonamides came into popular use) caused Rich[1] to suspect a nonspecific hypersensitivity reaction to sulfonamides. Rich[1,2] and Gregory succeeded in producing lesions resembling those of this disease in rabbits sensitized to horse serum. Ralston and Kvale[3] suggested that multiple etiologies were involved. Spink[4] described 2 cases that he considered to be related to penicillin.

It is probable that a hypersensitivity to serums, drugs and infections lies at the basis of the problem. However, Zeek et al.[6] have attempted to delineate "hypersensitivity angiitis" as an entity pathologically and etiologically distinct from periarteritis nodosa. Blankenhorn and Knowles[7] elaborated this concept and referred to 7 patients out of 10 with "hypersensitivity angiitis" who had a history of sulfonamide ingestion and 14 patients with periarteritis nodosa observed during the same period who had not previously taken sulfonamides.

Hydralazine Syndrome[8-12]

This syndrome has been described as occurring in patients successfully treated with the antihypertensive agent hydralazine hydrochloride (Apresoline). Lansbury and Rodgers[9] summarized phases that are similar to "rheumatoid arthritis" and "lupus erythematosus." This phenomenon occurred in 7.5 to 10.0 per cent of patients who received 600 mg. of hydralazine daily over periods averaging about twelve months. In most cases the syndrome developed as the diastolic pressure fell below 90. In some cases it appeared to be precipitated by intercurrent infection.

The "rheumatoid-arthritis" phase is characterized by chills and migrating arthralgia combined with myalgia. Later, there is frank arthritis, with symmetrical involvement of the proximal interphalangeal joints. If the drug is continued during this stage, the patient will progress to the "lupus-erythematosus" stage. If therapy is stopped the syndrome usually subsides, but it may be reactivated by readministration of the drug.

The "lupus-erythematosus" or febrile phase may be manifested by fever, prostration, pleural, pericardial or synovial effusions, cutaneous sensitivity to ultraviolet light, lupus-type rashes, splenomegaly and lymphadenopathy. Laboratory studies in the hydralazine syndrome may show decreased serum albumin, increased alpha-globulin and gamma-globulin fractions, increased sedimentation rate, transiently false-positive tests for syphilis, anemia, neutropenia and occasionally L.E. cells in peripheral blood or bone marrow.

Points of difference between the hydralazine syndrome and classic lupus erythematosus are as follows: remission in the former when therapy is stopped; only a small number of L.E. cells in the peripheral blood despite a full-blown clinical picture in the hydralazine syndrome; paucity of hematuria and proteinuria; and frequent recurrence of pneumonitis in the syndrome.

Interstitial Pulmonary Fibrosis

Interstitial pulmonary fibrosis, which resembles Hamman–Rich disease, nickel carbonyl poisoning or

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pulmonary scleroderma, has been reported by Turner and Lansbury[11] and others. It is believed to result from prolonged administration of the antihypertensive agent, hexamethonium. This syndrome is characterized by a relentless, progressive dyspnea that may result in death from acute fibrosis within thirty days of onset. The syndrome is reported as occurring in 5 out of 253 cases in one series receiving hexamethonium and hydralazine. Fourteen of these patients had the hydralazine syndrome in addition. Lansbury and Rodgers[9] cited 8 additional cases occurring in patients with malignant hypertension under hexamethonium therapy.

Neurologic Diseases

Epilepsy and Parkinsonism[13, 14]

A review by Barsa and Kline[13] of the use of reserpine in mental illness presented evidence that the onset of convulsive seizures or symptoms similar to those of Parkinson's disease, or both, was precipitated by treatment with this derivative of *Rauwolfia serpentina*. Grand-mal seizures occurred in 3 patients for the first time during their first six weeks on reserpine. Electroencephalograms revealed an epileptic pattern. In other patients who were epileptic or had been subjected to lobotomy there was an increase in the number of grand-mal seizures.

Reserpine has also been implicated in the causation of a syndrome suggestive of Parkinsonism with tremulousness, salivation, dizziness, paresthesias and so forth; this syndrome responded to methanesulfonate (Cogentin) and similar drugs. However, it must be added that cessation of therapy, decrease in dose or simple continuation of therapy caused these manifestations to disappear after a few weeks.

Psychoses[15-20]

Many drugs have been indicated as precipitating agents of toxic psychoses. Recent notoriety has come from the steroids and the Rauwolfia derivatives. Severe depressive reactions have been described, with a few reports of suicide.

Hepatic Coma

This is discussed below, under hepatic diseases.

Eighth-Nerve Damage

This is discussed below, under antibiotic-induced diseases.

Neuritides[21,23]

Many therapeutic agents have peripheral neuritis as a toxic side effect. Among these are arsenical compounds (also known to cause tubular vision) and mercurials. Stilbamidine is well known to be a cause of facial paresis and hypesthesias. Many varieties of serums also cause neuritis as part of the serum-sickness reaction.

Hepatic Diseases

Jaundice from Intrahepatic Obstruction[24-38]

This unusual syndrome has caused great confusion. Drugs implicated in this disease are chlorpromazine, arsphenamine, thiouracil, methimazole (Tapazole), methyl testosterone and atophan-cinchophen. In chlorpromazine jaundice the reported incidence is variable (3:71 and 1:506 cases, as well as 14 cases from the Mayo Clinic from a series of unknown size). The same mechanism seems to apply in each case. There is a definite increase in bile viscosity, with inspissation and plugging of the centrolobular biliary canaliculi. This results in an intrahepatic type of obstruction, with hyperbilirubinemia (primarily direct fraction), hypercholesterolemia (with normal esterification), excess of alkaline phosphatase in the blood and normal flocculation.

The diagnostic dilemma is obvious. The distinction between icterus of this variety and the jaundice of the intrahepatic phase of infectious or homologous-serum hepatitis, cholangiolitic biliary cirrhosis or frank extrahepatic obstruction is virtually impossible without liver biopsy.

Diagnosis is important since the prognosis of "drug-induced" jaundice is excellent owing to a minimal parenchymal reaction. This is true despite the fact that jaundice may persist for as long as three months.

Stolzer et al.[37] discuss another variety of jaundice that follows arsenical therapy. This is a delayed hepatocellular reaction in which the function studies are more compatible with inflammation or necrosis, or both, than with benign intrahepatic obstruction. It has been suggested that this represents a homologous-serum hepatitis from inoculation at the time of arsenical infusion.

Toxic Hepatitis[39-41]

Older drugs known to cause this disease include male fern, trinitrophenol (picric acid), dinitrophenol, gold compounds, chloroform, arsenobenzol compounds (salvarsan) and sulfonamides. Recently, a few new therapeutic agents have been reported to incite a toxic hepatitis. These are phenylacetyl urea (Phenurone), an antiepileptic, phenylbutazone (Butazolidin) and isonicotinic hydrazide.

Hepatic Coma[42-44]

The patient with decompensating cirrhosis can be thrown into hepatic coma by the injudicious selection of ammonium chloride as a diuretic to mobilize ascitic fluid, ingestion of a high-protein diet or the infusion of protein hydrolysate to replenish depleted serum protein. Davidson[42] considers it to be caused by hepatic inability to detoxify ammonia and believes that elevated ammonia levels are probably responsible for the cerebral syndrome of hepatic coma.

Hematologic Diseases

Hemotoxic Drug Reactions[45-49]

Dameshek[45] has delineated the varieties of hemotoxic reactions caused by drugs, as follows:

Antigranulocytic reactors. This disease was found to be a direct bone-marrow depression of granulocytic elements caused by drugs containing a benzene ring in combination with an amino or NH group.

Dinitrophenol — a notorious drug no longer used for weight reduction — also causes lenticular opacities.

Sulfapyridine — one of the early sulfonamides, succeeded by sulfadiazine and sulfisoxazole.

Antithyroid agents such as thiouracil, propylthiouracil and methimazole (Tapazole).

Phenylbutazone (Butazolidin) — the antirheumatic agent used in rheumatoid and gouty arthritis (this drug, along with cobalt, has recently been observed to cause thyroid hyperplasia with goiter by a mechanism in which it interferes with iodine uptake).

Antihistamines such as antergan and Pyribenzamine.

Chloramphenicol — a broad-spectrum antibiotic that fell into somewhat unfortunate disrepute, very effective against typhus and typhoid and, in combination with other antibiotics, against gram-negative organisms.

Streptomycin — an antibiotic effective alone and in combination against acid-fast bacilli and organisms refractory to other single antibiotics.

Antierythrocyte reactors. This reaction may occur by direct selective depression of erythropoietic elements (aplasia) or by autoimmunization of circulating red blood cells (hemolysis). Aplasia may simply be an early manifestation of a total depressant effect. Hemolytic drugs are: phenylhydrazine — previously used in polycythemia rubra vera (replaced by P_{32} and venesection); sulfanilamide — the first of the widely employed sulfonamides; and acetanilid — an antipyretic and analgesic that causes sulfanemia and methemoglobinemia, with secondary red-cell destruction.

Antiplatelet reactors. This reaction may also occur by direct bone-marrow depression of megakaryocytes as a forerunner of general bone-marrow depression, or by autoimmunization of circulating platelets; drugs that operate by the latter mechanism are Sedormid (a sedative and hypnotic derived from urea) and quinidine (a myocardial depressant used for ventricular and occasionally atrial arrhythmias). The clinical similarity of this syndrome to idiopathic thrombocytopenic purpura is striking. Again, phenylbutazone may initiate its toxicity through this mechanism.

Total bone-marrow reactors. The therapeutic agents implicated here cause unselective depression of all marrow elements. These include: amphetamine (Benzedrine), a sympathomimetic agent; antiepileptic drugs such as Tridione, Mesantoin and Dilantin; quinacrine (Atabrine), a malarial suppressant; phenylbutazone, an antiarthritic compound; and hydralazine, an antihypertensive compound.

Therapeutic application of this toxic effect has been employed in antileukemic and antileukosarcomatous agents. This brings up another "disease of medical progress," which is discussed below.

Anemias of Surgery

Iron-deficiency anemia.[50-56] Jasinski and Ott[50] described 39 patients with postgastrectomy symptoms that were thought to be caused by an alteration of pH that was due to loss of the hydrochloric-acid-producing portion of the stomach. This creates an environment unfavorable for the absorption of iron from foodstuffs since acidity is needed to convert the ferric hydroxide to ferric ion before reduction to the absorbable ferrous state.

Megaloblastic anemia. This syndrome has been reported to develop as late as two to five years after total gastrectomy. Several interesting reasons have been proposed for this delayed onset.

The first is incompleteness of the gastrectomy, with the result that a small amount of cardia (1.0 or 2.0 cm.) is left in situ to remain a source of sufficient intrinsic factor to permit normal utilization of vitamin B_{12} for several years.

The second is storage of erythrocyte maturation factor in the liver. The daily requirements of vitamin B_{12} being less than 1.0 microgm. per day (0.5 mg. per year), the liver stores of erythrocyte maturation factor may not become depleted for several years.

The third factor is prophylactic therapy. Virtually every postgastrectomy patient receives a multivitamin preparation for a prolonged period. Most of these capsules contain sufficient folic acid to prevent the emergence of a megaloblastic anemia for a considerable time. In most cases, however, the absence of any source of intrinsic factor prevents extrinsic factor from being absorbed, and the megaloblastic anemia appears.

In gastroenterostomy procedures the megaloblastic anemia that occurs has been related either to increased utilization of vitamin B_{12} by intestinal organisms that have been brought into proximity of the stomach or to decreased absorption due to pH changes caused by the operative procedure.

Metabolic Diseases

Secondary Gout and Uric Acid Calculi[57-64]

This interesting situation has been known to occur occasionally as a result of the breakdown of granulocytic and lymphocytic elements as well as

erythrocytes in the natural evolution of the leukemias and polycythemia rubra vera. The introduction of the newer antifolic acid compounds (aminopterin and amethopterin), as well as the newer purine analogues (6 mercaptopurine, thioguanine, 6 chloropurine and 2,6 diaminopurine), has created a situation in which the accelerated destruction of large volumes of cells releases an excessive amount of nucleoprotein. This in turn causes a rise in purine and pyrimidine concentration that reflects itself as a rise in blood uric acid. This high level may be associated with acute arthritic attacks, and the renal tubules may become supersaturated with urates. If the solubility threshold is exceeded, calculus formation may occur. A similar situation has been observed after the use of nitrogen mustard, tri-ethylene-melenamine (TEM) and radioactive phosphorus and in the early phases of therapy with the uricosuric agent probenecid (Benemid).

Retrolental Fibroplasia[65-70]

Pediatric progress has not been without its attendant woes. In response to the demands of the profession, manufacturers succeeded in producing incubators capable of delivering levels of oxygen higher than any previously attainable. Soon cases of mysterious blindness in premature infants began to occur in alarming volume. The disease was called retrolental fibroplasia.

Patz et al.,[68] employing ingenious animal experiments, proved that high oxygen concentrations resulted in an angioblastic outgrowth into the vitreous of fine capillary vessels deriving from the vasculature of the developing retina. This process eventually proceeded to retinal detachment and blindness.

The exact pathogenesis remains obscure. However, the lesion may lie in the oxygenation of hydrogen from sulfhydryl groups of critical respiratory enzymes. And this, paradoxically, is a true cellular anoxia caused by oxygen.

Low-Sodium Syndromes[71-75]

This variety of illnesses has become possible since the development of effective low-sodium diets and the skillful use of more powerful diuretic agents. Several types of the "therapy-induced" diseases are known. These are as follows:

True plasma sodium depletion is the most commonly encountered variety. It is characterized by muscular cramps, nausea, anorexia, drowsiness and weakness. This is followed by diminution of renal blood flow, with a drop in urinary output and nitrogen retention. It is a close step to uremia.

Dilution hyponatremia is a syndrome that may be fatal. Patients with long-standing congestive heart failure exist in a state of moderate cellular anoxia. In this situation a change in cellular responsiveness to osmotic alteration occurs. The patients are incapable of responding to this altered electrolyte state (hyponatremia) when hypertonic saline solution is administered. Uricchio and Calenda[74] presented 7 cases of dilution hyponatremia, all demonstrating unresponsiveness to hypertonic saline solution, with fatal outcome. The clinical differentiation of true sodium depletion and sodium dilution is quite difficult.

Digitalis-Induced Gynecomastia[76]

The chemical similarity of the digitalis glycosides to estrogenic compounds has been cited as the cause of the disturbing development of gynecomastia in some patients on digitalis therapy.

States Similar to Cushing's Disease

These are discussed below under steroid-induced diseases.

Adrenal-Exhaustion Syndrome

This is discussed below under steroid-induced diseases.

Steroid-Withdrawal Syndrome

This is discussed below under steroid-induced diseases.

Hyperchloremic Acidosis

This is discussed below under surgically induced diseases.

Goiter Induced by Phenylbutazone and Cobalt[77]

The development of thyroid hyperplasia in patients receiving phenylbutazone for arthritis or cobalt for anemia has been described. It is considered to be due to interference in the iodine-trapping mechanism.

Surgically Induced Diseases

Anemias of Surgery

These are discussed above, under hematologic diseases.

Hyperchloremic Acidosis[78-80]

The transplantation of the ureters into the bowel as a method of bladder by-pass has become an important procedure in the management of exostrophy or cancer of the bladder. And again, as a result of this surgical advance, a new illness has emerged.

With the emptying of the urine into the rectosigmoid, sodium chloride and ammonium chloride are reabsorbed in varying amounts. This results in an excess of chloride in the plasma. This in turn displaces bicarbonate, which is readily compensated for by carbon dioxide excretion through the lungs, resulting in a drop in blood pH. This is hyperchloremic acidosis. Some authors believe that this situation cannot occur without pre-existing renal damage.

Normochromic anemia and transient disturbance

of carbohydrate metabolism have also been found to attend hyperchloremic acidosis secondary to ureterosigmoidostomy.

Dumping Syndrome[81-83]

The familiar symptoms of fullness and churning in the epigastrium, followed by or associated with weakness, sweating, tachypnea, tachycardia, pallor and transient hypertension, constitute another classic disease of "surgical progress." It is apparent that this is a sympathetic response, but the mechanism has remained obscure. Roberts et al.[81] have shown that the ingestion of a hypertonic solution in a partially gastrectomized patient will produce the dumping symptoms. This is considered to be due to the fact that the rapid passage of the undiluted, hypertonic food from stomach to jejunum causes a sudden dilution of the intraluminal material by interstitial and intravascular crystalloids, with an acute loss of circulating blood volume. This is akin to a "cell-less hemorrhage" and produces a shocklike state.

Another postulated mechanism is that the acute distention of the jejunum may cause mechanical stimulation of the adjacent splanchnic nerves and trigger a sympathetic response.

Finally, the role of potassium in "dumping" has not been clearly defined. It is suggested that a rapid shift of ionically active potassium into storage occurs as ingested glucose is metabolized and stored as glycogen. This results in an extracellular deficit. Clinical response to oral administration of potassium has been observed repeatedly, but the mechanism has yet to be proved to complete satisfaction.

Antibiotic-Induced Diseases[84-95]

These "diseases of medical progress" have been the subject of innumerable papers in recent years. The common denominator of most members of this group is the disruption of the normal ecologic balance of the gastrointestinal tract, with destruction of susceptible organisms permitting overgrowth of resistant organisms. Once this homeostatic balance is disturbed, organisms (bacteria and fungi) that were previously benign may become quite virulent. These entities were practically unknown before the antibiotic era.

Diseases Caused by Resistant Staphylococci[85-88]

The well established fact relating to the antibiotic-resistant staphylococcus has many clinical ramifications.

Staphylococcal septicemia and endocarditis. Spink points up the acuteness of this problem by citing 7 cases of staphylococcal septicemia occurring in one week in two Minneapolis hospitals. Four of these patients had an associated acute endocarditis. All the infections arose in the course of antibiotic therapy for other diseases.

Pseudomembranous enterocolitis. This complication has been known for a long time. Dixon and Weisman reported 23 cases occurring before 1947 (pre-antibiotic era). However, the incidence of spontaneous cases is generally low. The relation of antecedent bowel surgery (especially for carcinoma of the colon) is well established. Dearing and Heilman believe that the use of oxytetracycline and chlortetracycline has been related to pseudomembranous enterocolitis. They cite the rise in incidence since the widespread use of antibiotics. These act by destruction of susceptible flora, the resistant staphylococcus gaining ascendancy and massively invading the bowel wall.

Staphylococcal diarrhea. Virulent debilitating diarrhea, with stool cultures yielding resistant staphylococci, has been reported to occur at the extremes of age after the use of broad-spectrum antibiotics.

Staphylococcal pneumonia. The emergence of this severe interstitial pneumonitis in the wake of a clearing pneumonia is a most disturbing event.

Anorectal Syndrome[89,90]

The annoying, burning pain, pruritus and occasional melena that follow the use of the broad-spectrum antibiotics have come to plague proctologists. The anorectal syndrome is variable in its severity and is thought to be quite common. A direct action on the bowel wall has been postulated as the mechanism involved. It is resistant to therapy and often persists for months after the offending agent has been stopped.

Candida albicans Infections

Stomal and cutaneous ulcers, pneumonia and diarrhea due to monilia follow disruption of normal ecologic balance, after antibiotic therapy. Although these infections are not as frequent as suspected previously, they continue to appear, especially in debilitated patients.

Gram-Negative Bacteremia

The increasing frequency of bacteremias due to *Escherichia coli, Aerobacter aerogenes, Proteus vulgaris* and paracolon organisms is also related to the selective depression mechanism cited above.

Deficiency of Vitamin K and B Complex

The destruction of colon bacilli engaged in the synthesis of vitamin K and B complex by prolonged antibiotic therapy has been described. Smith reported a case of pellagra associated with pulmonary moniliasis in an elderly woman given chlortetracycline over a thirty-day period.

Neurologic Disturbances

Operating by a different mechanism from that observed in the illnesses noted above, paresthesias of the hands, tongue, and circumoral areas have been

described after streptomycin and polymyxin administration. These symptoms may persist for prolonged periods. Intramuscular injection of streptomycin has been followed by a severe peripheral neuritis in the injected extremity.

The well known ravages of streptomycin on the eighth nerve (causing vestibular dysfunction) and of dihydrostreptomycin (causing deafness) need little comment.

Serum-Sickness Reaction[95]

The sowing of the wild oats in the early penicillin era is yielding its harvest with increasing reports of serum-sickness types of reactions. The more critical anaphylactic reactions have also become more numerous. By good fortune, for the most part, the angioneurotic edema, urticaria and arthritis of this illness respond well to steroid therapy.

This outline is not complete, but will give some idea of the unwondrous woes that have followed in the wake of the "wonder" drugs.

Steroid-Induced Diseases[96-121]

States Similar to Cushing's Disease

In the process of long-term steroid therapy for severe illness (rheumatoid arthritis, lupus erythematosus and asthma), the effectiveness of the drug often does not become manifest until dosage is pushed to a point where signs of toxicity resembling Cushing's disease may appear quite insidiously. Hypertension, mental torpor, hyperglycemia with glycosuria, sodium retention and potassium loss, acne, buffalo hump, hirsutism and a negative nitrogen balance with muscle wasting and osteoporosis may also occur. The full constellation or any individual sign may be the presenting complaint.

"Adrenal-Exhaustion Syndrome"[120]

Salassa et al.[120] have reported on this problem. They present conclusive evidence that steroid therapy (cortisone or ACTH) is capable of inducing adrenocortical atrophy. Steroid-treated patients run a definite risk of succumbing to "adrenal exhaustion" at the time of some future stressful situation (such as surgery, parturition, accident or burn). The limits of time from therapy to onset of stress and dosage are not clearly defined. However, as little as 100 mg. given over a five-day period has been suspected of causing significant adrenocortical suppression. It seems "safest to assume that any patient who has received cortisone in significant quantities within three to six months should receive prophylactic therapy" and "any patient who has had severe hyper-corticism within one and one-half years before operation . . . should be treated."[120] Tests of adrenocortical function may be useful in preoperative evaluation if they reveal adrenal unresponsiveness, but a negative test may not be a true index of what the gland will do in response to actual stress.

Many surgical services now make careful inquiry into the steroid history of a person who is scheduled for an operation. When it is discovered that the patient has received steroids in the past, a definite routine is followed. This consists of tests of adrenocortical function when feasible, administration of hydrocortisone before and after operation and meticulous attention to the course in the first twelve hours after operation.

It may be advisable to have any patient who has been treated with steroids carry a card describing the dose, duration and variety of steroid and a statement of why it was employed.

Steroid-Withdrawal Syndrome[121]

Henneman et al.[121] recently reported 19 cases in which steroids were withdrawn abruptly after prolonged administration. Within twenty-four hours nearly all patients had headache, nausea, vomiting, restlessness and muscle and joint pain. Symptoms subsided spontaneously in three to five days. This was believed to resemble mild adrenal crisis.

Peptic Ulcer and Perforation in Regional Enteritis and Ulcerative Colitis[99-114]

Cortisone, hydrocortisone, the halogenated corticoids, metacortandralone and phenylbutazone have all been implicated as causative factors in subtle (often asymptomatic) peptic ulceration or perforation or both.

Bunim reports 3 cases of peptic ulcer developing in 71 arthritic patients, with 2 perforations. It was significant that these were the only 3 patients in the entire series who had been maintained on daily doses of cortisone as high as 100 mg.

Lukewarm reports on steroid therapy in regional enteritis have been punctuated by reports of perforation.

Enthusiasm for the use of steroids in the management of ulcerative colitis has been somewhat tempered by a significant incidence of bowel perforation. In many series there are no reported perforations, but in others the rate of occurrence has been 3:17, 3:15 and 1:8.

Cardiac Diseases

Arrhythmias[122-125]

Lown and Levine[122] have described the problem of digitalis-induced arrhythmias. When the digitalis glycosides are used according to a fixed dosage schedule unrelated to weight, size and clinical condition of the patient, many types of arrhythmias may develop. The capacity of digitalis intoxication for mimicking any type of arrhythmia is all too well known. These range from paroxysmal atrial tachycardia with

block to ventricular tachycardia. These arrhythmias may be attributed erroneously to the underlying heart disease.

Quinidine, by virtue of its ability to depress myocardial irritability, can cause sudden and severe increases in ventricular rate when used to slow atrial fibrillation. Spontaneous ventricular tachycardias have also been attributed to quinidine.

Procaine amide (Pronestyl) has come in for some bad publicity by virtue of its ability to produce ventricular tachycardia and fibrillation.

Again, Rauwolfia is reported to have caused premature ventricular contractions.[125]

Hemorrhagic Pericardial Effusion[126-131]

The widespread use of bishydroxycoumarin and related anticoagulants in cases of acute myocardial infarction has resulted in a syndrome of pericardial effusion apparently due to diapedesis of red cells from the fragile capillaries of the subepicardial infarcted myocardium. Actual acute tamponade requiring emergency pericardiocentesis has occurred.

Nonspecific Myocarditis[132]

This entity has been attributed to many causes, among which are drugs. Most notable among these are emetine, Fuadin, tartar emetic, and sulfadiazine.

Renal Diseases

Acute Renal Shutdown (Acute Tubular Necrosis, Lower-Nephron Nephrosis)[133,134]

The classic studies by Lucke,[133] supplemented by the large series of Swann and Merrill,[134] pointed out that therapeutic agents such as blood (incompatible) and sulfonamides (without proper alkalinization and hydration) can cause renal failure. This, of course, is in addition to the more common offenders such as prolonged shock and myoglobin from crush injuries.

Drug-Induced Nephroses[135-138]

A nephrotic syndrome has been reported to follow the therapeutic application of Tridione, Paramethadone, the chelating agent sodium ethylene diamine tetra-acetate and hypertonic solutions of sucrose, glucose, acacia and urea.

Acute Urinary Retention[139-142]

This is certainly not a disease, but may be an embarrassing complication if the cause is not recognized in a patient under therapy with one of the autonomic blocking agents such as methantheline (Banthine), hexamethonium, pentapyrrolidinium (Ansolysen), dibenamine and others.

Dermatitides[143,144]

This is probably the oldest area of "disease caused by drugs." This list is quite lengthy without going into dermatitis medicamentosa. One may now add the urticaria of penicillin-induced serum sickness along with the classic members, phenolphthalein, arsenic compounds, gold, iodides, mercurials, barbiturates, salicylates and sulfonamides.

Conclusions

Needless to say, in this brief review, it has been impossible to cover and amplify all the diseases that have appeared as the result of progress in medicine. I am sure that every physician could add a few to the list. However, this subject is not unique to medicine. Progress in every sphere of human endeavor creates new problems at each turn. At times this may be discouraging, but it is never dull.

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MEDICAL INTELLIGENCE

A NEW, EFFECTIVE SHAMPOO TREATMENT IN SEBORRHEA CAPITIS

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SEBORRHEA capitis, especially the dandruff or "sicca" type, is believed to affect almost everyone, in some degree, through a good part of adulthood. Since the condition is not disabling only the severe cases come to the attention of the physician. However, it has been reported[1,2] that 25 per cent of all dermatologic patients seen in private practice suffer with seborrheic disturbances, seborrhea capitis and acne vulgaris being by far the most common. Dandruff, seborrhea oleosa and seborrheic dermatitis are therefore of at least quantitative importance to the physician.

Treatment of seborrhea capitis should be not only effective but also simple, easily applied and harmless. There is no real "cure" for seborrhea. Treatment should therefore be effective in clearing the scalp and skin of the oiliness, scaling and crusting during the acute phase, as well as in preventing their recurrences thereafter.

Treatment has heretofore consisted of combinations of mercury, sulfur, tar, resorcinol and salicylic acid in ointment or lotion form. Although these are usually effective and are very useful during the acute phase, they are quite messy. Patients eventually rebel against them, particularly for maintenance therapy. The introduction of selenium sulfide shampoo[3-5] greatly simplified the treatment of dandruff. However, its potential toxicity, its stimulation of sebaceous secretions, thereby making the scalp oily,[5] and its occasional orange tinting of gray hair and causing of hair loss[6] are drawbacks to its use. Furthermore, selenium sulfide is not effective for removing exces-

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sive oiliness in seborrhea oleosa, which is often seen in association with acne vulgaris.

The three main therapeutic actions essential in the control of seborrhea capitis are as follows: reduction of excessive oiliness (degreasing or "drying" effect); keratolytic action to remove the keratotic blocking of the pores (peeling effect); and germicidal action to minimize secondary infection. This report is about a new, simple, easy-to-use treatment that embodies these three essential therapeutic actions.

New, Simple Treatment

The new treatment for seborrhea capitis is used as a lathering cream shampoo.* It consists principally of a combination of anionic surface-active agents — detergents and wetting agents selected, during a series of preliminary clinical trials, for optimum antiseborrheic efficacy. These anionic agents consist of sulfoacetate, sulfonate and sulfosuccinate, all of them employed in dermatology for years with a documented record of safety and tested for absence of toxicity and irritant and sensitizing properties.[7-10] The combination has profound antiseborrheic, penetrating action and is mildly keratolytic and antibacterial. Further keratolytic and antibacterial action is provided by micropulverized sulfur, 2 per cent, salicylic acid, 2 per cent, and hexachlorophene, 1 per cent.

Table 1 shows the interlocking, mutually reinforcing action of the constituents of the cream shampoo.

Table 1. *Composition of the Cream Shampoo.*

Action	Constituents			
	Sebulytic	Hexachloro-phene	Sulfur	Salicylic Acid
Antibacterial	+	+	+	+
Keratolytic	+	−	+	+
Antiseborrheic	+	−	−	−

Directions for Use

Patients are instructed to use the antiseborrheic cream as a shampoo as follows: a liberal amount of the cream is massaged into the wet hair and scalp for five minutes; this is followed by a rinse; another portion of the cream is massaged into the hair and scalp for five minutes; the patient then rinses with warm and then with cool water.

Frequency of Application

The cream shampoo should first be used every three or four days. The interval between shampoos should be prolonged as the obtained reduction of oiliness and scaling permits. Once these are controlled the scalp can be maintained clear with a shampoo once a week or less often.

*Fostex Cream, kindly supplied by Westwood Pharmaceuticals, Buffalo, New York.

Clinical Evaluation

The effectiveness of Fostex Cream in the treatment of seborrhea capitis and seborrheic dermatitis was studied clinically in 251 patients. One hundred and twenty-two were female, and 129 were male. In 173 cases the diagnosis was dandruff or seborrhea "sicca." Twenty-nine of these had associated seborrheic dermatitis. In 49 patients the diagnosis was seborrhea oleosa. Most of these cases of seborrhea capitis were severe — with heavy scaling, invariably of many years' standing. The patients also had been treated, at home or by the family physician, with many and varied topical medications.

Table 2. *Statistical Data in 251 Cases.*

Datum	No. of Cases
Sex:	
Female	122
Male	129
Age distribution:	
10-20 yr.	96
20-40 yr.	119
>40 yr.	36
Diagnosis:	
Seborrhea sicca	173
Seborrhea sicca, with dermatitis	29
Seborrhea oleosa	49
Duration of treatment:	
0-4 wk.	2
4-12 wk.	127
>12 wk.	122
Result:	
Excellent	208
Good	34
Fair	6
Poor	3
Side effect:	
Too drying	3

During the acute phase of the condition the patient was treated with topical medication designed to support the antiseborrheic shampoo. Just as soon as the acute phase subsided all such topical medication was stopped. Fostex Cream was continued as the sole treatment for the control of the remaining symptoms and for preventing their recurrence.

Results

Results ascribed to the antiseborrheic shampoo were considered excellent in 208, good in 34 and fair

in 6 cases. Three patients complained of excessive dryness from the shampoo, and it had to be discontinued. These were the only patients who failed to benefit from Fostex Cream.

The antiseborrheic shampoo dries the scalp and removes scales quickly. The drying effect is so pronounced as to be excessive in some dry scalps, especially when other topical medication is used. In seborrhea oleosa I have observed Fostex Cream to be the only available medication that is really helpful in removal of excessive oiliness. Every case of seborrheic dermatitis cleared completely, perhaps because of the control of dandruff, which is assumed[11] to be a primary underlying cause of this condition.

Patient co-operation was excellent because of the simplicity of the antiseborrheic shampoo. Patients were particularly enthusiastic about their ability to prevent recurrences of symptoms with one shampoo a week or less often.

Statistical data are presented in Table 2.

Summary

A new, easy-to-use shampoo treatment for seborrhea capitis is described. This combines anionic detergents and wetting agents chosen for optimum antiseborrheic properties, with sulfur, salicylic acid and hexachlorophene.

The new treatment is at least 95 per cent effective in the control of dandruff, seborrhea oleosa and seborrheic dermatitis. It is relatively nontoxic and is remarkably free of irritant properties. In some dry scalps, however, it can produce excessive dryness. Patient acceptance of this cream shampoo is excellent.

510 Commonwealth Avenue

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BY THE LONDON POST

In Brighton and London — Early to Rise

John Lister, M.D.

London, England

BRITAIN has no Atlantic City but Brighton provides a fine conference city by the sea and it was there that the British Medical Association held its annual conference this year.

Because a certain Dr. Richard Russell was the founder of modern Brighton the city has had a long association with medicine. In 1750 Dr. Russell published a book entitled, *A Dissertation on the Use of Sea Water in the Diseases of the Glands.* In this he advocated sea-bathing as a form of treatment for many complaints, and patients soon came from all over England to take the sea-water cure. In 1784 the Prince of Wales visited the resort, for he had been advised to take sea bathing for his health. Brighton's later prosperity, started by this royal patronage and by the patronage of the physicians and their patients, has depended on successive generations of trippers, who have arrived from London and much farther afield in coaches, trains and motor cars.

It is nearly fifty years since the British Medical Association last visited Brighton, but this most recent visit has been acclaimed a great success. In his presidential address the incoming president, Dr. Alexander Hall, himself a general practitioner and only the third general practitioner to become president of the Association in fifty years, spoke on the state of general practice today. He pointed out that in this country the general practitioner is the family doctor who should provide the first line of medical defense in all matters of health — both prophylactic and therapeutic. The traditional medical etiquette of the country is such that no direct approach is made to consultants and specialists and that it is part of the duty of the family doctor to direct his patients to the right consultants when special advice is required. At the same time he must survey the patient as a whole and be responsible for the continuity of his case.

In spite of the great responsibility that thus falls on the general practitioner and in spite of repeated pronouncements by officialdom that the general practitioner must remain the kingpin of the Health Service, Dr. Hall thinks that all is not well with the general-practitioner service. Admitting that he possibly holds a reactionary view, he believes that the status of the general practitioner has been lowered by the conditions of the Health Service. The general practitioner has virtually no access to hospital beds, often little access to laboratory and x-ray facilities and virtually no opportunity to graduate to consultant status as he could in days gone by. For

the sake of organizational expediency the general-practitioner and consultant services have been split and much of the work that family doctors should undertake is passed on to hospital clinics. These points have all been recognized by the "planners," but Dr. Hall sees little evidence of any moves to correct the matter. Furthermore, he believes that medicine is in danger of losing its dynamic character and becoming standardized in all respects. This he attributes to the contracting field of freedom in practice. He believes that for a high standard of practice to be maintained it is essential that there be continuing opportunities for freedom to practice private medicine outside the National Health Service. These views have all been stressed before, and though outspoken they are stimulating and calculated to maintain a live spirit in the British Medical Association.

In his concluding remarks Dr. Hall applauded a paragraph from an essay in the *Times Literary Supplement* earlier this year that referred to "an old fashioned society, inherited without much self-questioning, but nevertheless a society that still offered opportunities to the young and the talented and the enterprising — not a society harried, hag-ridden by regulations and financially penalized." Times have changed — but if the medical profession in any country is to remain dynamic, it must offer opportunity to the young and the enterprising. Only if it does so will the medical profession be able to live up to the words of the first Brighton president of the Association, who said, in 1851, that "In all positions of honour men are excited to do their best."

The Conference scene moved swiftly from Brighton to London, where the fifth International Congress of Gastro-enterology was held later in the month of July. Delegates came from all over the world and were treated to a well balanced diet of banquets, civic receptions and scientific sessions. The Congress was opened at the Royal College of Surgeons by the Minister of Health, Mr. R.H. Turton. He commented that gastroenterology provides a common meeting ground for surgeons, physicians and radiologists. Furthermore, he said, the subject has an even wider appeal because in no other branch of medicine is the ordinary citizen, with his overindulgence in eating and drinking, willing to be so happy a provider of clinical material. The scientific sessions covered a wide range of subjects, the main topics being ulcerative colitis, premalignant conditions of the alimentary tract and benign conditions of the esophagus. Differing views were freely expressed and provided a stimulating atmosphere for the Conference.

The social occasions included receptions by the British Government, London University and the Royal College of Physicians, and, on the final night, a banquet was held in the Guildhall in the City of London. This last occasion provided a fitting conclusion to the great conference, and the delegates heard a series of memorable speeches from such eminent men as the Lord Mayor of London, Lord Adrian, O.M., Dr. Thomas Hunt, the president of the Congress, and Dr. Arthur Douthwaite.

* * *

Probably the greatest shock that any Englishman receives when he visits the United States is the inevitable invitation to keep an office appointment at eight o'clock in the morning. He knows that work starts at that hour, but somehow it always comes hard the first time. I once discussed this with an American friend whom I first met when he held a fellowship at Cambridge. I was surprised when he told me how hard he found it to be punctual for nine o'clock lectures at Cambridge, but he explained it easily. His Cambridge college rooms had no central heating, and until his servant had started the coal fire in the morning it was too cold to get up! I doubt whether it is really quite so simple, and I suspect that there are other factors — one of which I am sure is the meal called breakfast. It is a meal I once heard scorned by an American professor of medicine. His students had pleaded lack of time as an excuse for not having worked up their cases for his eight o'clock round. He questioned their habits and asked them how they spent that hour between seven and eight o'clock in the morning. To his apparent horror they said that that was when they ate breakfast. To this he replied that his cases were more important than their breakfasts and that if they could not cope with both, they must go without breakfast. The reputation of the English breakfast is, of course, well known. It is aromatic, substantial and gratifying to the inner man. It is a time when the mail and the papers are read, and plans for the day are made — and all at a leisurely pace. Some streamlining has inevitably resulted to keep up with the general acceleration of life, but the traditional facts remain. Only once a year is the pattern altered, and this is the day when the family departs for its annual vacation. On this occasion, it is no hardship to rise before dawn, have only tea and toast and be driving on the open road long before daylight. Only recently, while driving up the Great North Road to Scotland, well before six o'clock in the morning, I wondered why we so persistently waste those precious hours before nine o'clock. Perhaps we should make a real effort to heat our homes and learn to do without our English breakfast and then we should always be ready for work at eight o'clock. On the other hand, perhaps we should not try to alter what is, after all, just another old custom, and perhaps we should just agree to differ — eight o'clock in your country and nine o'clock in ours.

CASE RECORDS
OF THE
MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

BENJAMIN CASTLEMAN, M.D., *Editor*

VIRGINIA W. TOWNE, *Assistant Editor*

CASE 42391

PRESENTATION OF CASE

A sixty-three-year-old woman entered the hospital because of pain in the back.

Four days previously she noted persistent soreness over the lower portion of the back, anorexia, a sore throat and a temperature of 103°F. The next day there was also abdominal soreness that involved both lower quadrants. On the day of admission there was very severe pain in the lower back; the temperature was 101°F. There were no urinary symptoms, nausea, vomiting, diarrhea, jaundice or melena.

A right-sided inguinal herniorrhaphy was performed eighteen years before admission at another hospital.

Physical examination revealed a well nourished woman who complained of pain in the back. The throat was slightly inflamed. The chest was normal. Examination of the abdomen showed tenderness over the entire right side, with maximum tenderness, rebound tenderness and spasm in the subcostal region. Peristaltic sounds were normal. No masses were felt. There was a healed herniorrhaphy incision on the right. Rectal examination was negative.

The temperature was 100°F., the pulse 92, and the respirations 20. The blood pressure was 142 systolic, 70 diastolic.

The urine gave a ++ test for albumin; the sediment contained 3 red cells, 8 white cells and an occasional granular and hyaline cast per high-power field. Examination of the blood revealed a hemoglobin of 12.8 gm. per 100 ml. and a white-cell count of 20,800, with 79 per cent neutrophils. The serum bilirubin was 1 mg. per 100 ml. The amylase was 4 Russell units, and the phosphatase 1.8 units. X-ray films of the chest demonstrated a slight increase in pulmonary vascular markings, slight left ventricular prominence and slight elevation of the right leaf of the diaphragm. Films of the lumbar spine and pelvis showed slight osteoporosis and some calcification of the wall of the abdominal aorta. An intravenous pyelogram was normal. A lumbar puncture yielded clear cerebrospinal fluid under an initial pressure equivalent to 140 mm. and a final pressure equivalent to 90 mm. of water; there was 1 lymphocyte per cubic millimeter; the total protein was 24 mg. per 100 ml., and the gold-sol curve 1122100000; a culture was negative.

The pain in the back diminished whereas the abdominal pain increased. Nausea was noted. Abdominal spasticity and tenderness persisted in the right upper quadrant. On the first hospital day the point of maximum tenderness lay to the right of the umbilicus. The temperature ranged between 99 and 100°F. On the next day an exploratory laparotomy and appendectomy were performed. No abnormalities were noted. The postoperative course was uneventful until the fifth postoperative day, when the patient collapsed while on a bedpan. She appeared cold and clammy and complained of pain in the back and shortness of breath. The blood pressure was 80 systolic, 50 diastolic. The pulse was rapid and thready. Subsequently, she became pale, flaccid and unresponsive and died about an hour later.

DIFFERENTIAL DIAGNOSIS

DR. WILLIAM R. WADDELL*: I should like to supplement the information given in the protocol by looking at the x-ray films.

DR. JOSEPH HANELIN: There certainly is no abnormality in the chest; even the slight elevation of the right leaf of the diaphragm is quite normal. The heart at the most is borderline in size but is probably slightly enlarged along the left ventricle. You may be interested in the status of the thoracic aorta, which does not seem to be unduly wide. The pyelogram is normal. In the lateral film of the spine there is calcification in the wall of the abdominal aorta as it overshadows the upper lumbar area; some mild widening of the abdominal aorta is indicated by the position of the calcification. The bones themselves are within normal limits.

DR. WADDELL: Unless there was some obvious reason for omitting the examination of the legs, particularly their vessels, I wonder if Dr. Welch would comment on them.

DR. CLAUDE E. WELCH: The vessels in the legs were all normal. They were examined carefully daily; the pulses remained regular and normal throughout the course.

DR. WADDELL: I think that there is no getting away from the patient's principal complaint of pain in the back, which was apparently associated with a febrile illness. The sore throat gives some indication of the

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possible source of the fever, although it may have been more directly related to the pain. The fever apparently subsided during the twenty-four hours that she was observed, but I gather that the back pain continued to be an impressive feature of the illness, leading to a lumbar puncture and an intravenous pyelogram. I can attribute no significance to the abnormal gold-sol curve of the spinal fluid. A great many conditions are associated with so-called first-zone reaction, and I see no clue that would lead to a diagnosis on the basis of this abnormality. The physical examination, I think, is important, particularly since the symptoms were principally related to the back and lower abdomen; the physical findings involved the lower abdomen to a slight extent but were mainly confined to the upper abdomen.

The laboratory data deserve some comment; the urinalysis is consistent with chronic renal disease. The thought of acute nephritis associated with a sore throat comes to mind, but I think that is unlikely because of the nature of the sediment. Three red cells are often observed in the urines of normal patients in routine examinations. Furthermore, I should expect more than an occasional cast and in addition red-cell casts. Therefore, I shall exclude renal disease from further consideration. The serum bilirubin was slightly elevated, but the phosphatase indicated no obstruction of the biliary tract.

Since back pain was the predominant complaint of the patient and was obviously the concern of those who were caring for her, I think a differential diagnosis of this symptom is warranted. In that differential diagnosis I should place a renal stone as the most common on a statistical basis. That has been excluded by the normal intravenous pyelogram and the course of events, which certainly indicated that something more than the passage of a renal stone was bothering the patient.

Numerous pathologic conditions of the spine itself are possibilities, but there seems little to draw one toward a diagnosis of tumor, metastatic abscess, tuberculous infection or even acute ruptured intervertebral disk.

Pain in the back is often associated with vascular abnormalities. Because the patient demonstrated an abnormality of the lower abdominal aorta, — calcification, — it is worth while to consider the possibilities of dissection of the aortic wall, aneurysm, which if present, was small, since it was not palpated, and acute thrombosis of the lower end of the aorta. Calcification of the aorta is a common condition and certainly not diagnostic, but in its presence the index of suspicion that this area was a site of the difficulty should be increased. The information given by Dr. Welch that the distal arterial system was normal, and remained so, excludes certain of these diagnoses. Thrombosis of the lower end of the aorta is not compatible with those findings, nor is dissection of the lower end of the aorta. Moreover, dissection occurs principally in the thoracic aorta and it is associated with hypertension in the vast majority of patients.

The patient obviously had an upper respiratory infection, and I think some of the findings can be explained on that basis. I should have considered acute cholecystitis or appendicitis as the most likely preoperative diagnosis. Pancreatitis is unlikely, unless it was low grade, principally an inflammatory reaction without fat necrosis or hemorrhage.

One other condition worth mentioning, although I see no way in which it can be related to all the events of the illness, is the possibility that the pain in the upper abdomen was related to the pulmonary infarcts and that the final illness was a fatal large pulmonary embolus. That would leave the original complaint and one of the important features of the illness — pain in the back — totally unexplained, unless it could be related to the acute respiratory infection. We have all experienced some degree of myalgia with a respiratory infection, and occasionally this can be relatively strenuous, although I doubt if it would have been described as very severe by the examiner.

The negative laparotomy immediately excludes any of the diagnoses that I have mentioned. Therefore, I am in the position of suggesting either that one of the surgeons did not carefully examine the abdomen or that the disease was unrelated to an intra-abdominal condition that could have been discerned at operation. Even acute vascular conditions, such as thrombosis of the aorta, can be recognized by a simple palpation of the vessels distally. My guess, then, is that the patient had low-grade pancreatitis of a sort that was difficult or impossible to ascertain at operation. I think that death resulted from a pulmonary embolus.

Dr. Richard B. Cohen: Dr. Chapman, have you a comment?

Dr. Earle M. Chapman: I am not going to risk my batting average, but I shall call on Dr. Henry Fox, a visitor, whose opinion I share.

Dr. Henry Fox: I do not believe that the possibility of a small dissecting aneurysm is ruled out. The mechanism of death in itself — the woman was on a bedpan straining, when she suddenly collapsed, became pale, sweated, with a thready pulse, and died — certainly suggests a vascular accident. I think the aneurysm involved the thoracic aorta and extended to the upper abdominal aorta and that it suddenly ruptured retroperitoneally.

Dr. Victor G. Balboni: When I first saw the patient on the day I sent her to the hospital, she was having such severe pain in the back that to get out of bed she had to roll over and crawl out on her hands and knees; yet straight-leg raising did not aggravate the pain, and flexion of the thighs on the lumbar spine allowed the lumbar spine to move. She did have abdominal pain that morning.

Dr. John A. Benson, Jr.: I should bet on the dissecting aneurysm.

DR. COHEN: Would you tell us the preoperative opinion, Dr. Welch?

DR. WELCH: The preoperative diagnosis was a question of stone in the common duct.

I think that this case brings out the limits of exploratory laparotomy. The surgeon never can do as complete an examination as the pathologists can do later. We did a careful exploration; I was satisfied that we had excluded disease of the biliary tract; the pancreas felt normal. I was particularly interested in the character of the abdominal aorta. It pulsated perfectly normally both above and below the pancreas, and both the iliac arteries pulsated. When the transverse mesocolon was turned up, there was no evidence of hematoma or of hemorrhage in the retroperitoneal tissues. The aorta was not exposed from one end to the other, but that maneuver is a very complicated procedure.

DR. GEORGE S. RICHARDSON: I think it was a most thorough laparotomy.

CLINICAL DIAGNOSES

Gastroenteritis.
Pulmonary embolus.

DR. WILLIAM R. WADDELL'S DIAGNOSES

Pancreatitis.
Massive pulmonary embolus.

ANATOMICAL DIAGNOSES

Ruptured mycotic aneurysm of abdominal aorta.
Retroperitoneal hemorrhage, massive.
Acute bacterial endocarditis, aortic valve.

DR. COHEN: The disease, as has been suggested, was localized in the cardiovascular system. The most striking finding at autopsy was a relatively recent, massive retroperitoneal hemorrhage. The source of this hemorrhage was a disruption of the aortic wall posterolaterally immediately below the level of the renal arteries. The aorta at this level was severely atherosclerotic and slightly dilated. Numerous atherosclerotic ulcers were noted, and calcification was marked. At the site of the tear there was a large, reddish-brown, friable ante-mortem clot. Another relevant finding at autopsy was a large, friable thrombus, 1 cm. in diameter, on the anterior cusp of the aortic valve. Microscopical examination of this vegetation and valve confirmed the fact that this was a bacterial endocarditis of relatively acute nature, with numerous neutrophils infiltrating both vegetation and valve substance. Microscopical examination of the aortic wall at the site of the tear revealed an intense neutrophilic infiltration, and the clot adherent to the wall at the site was identical to that on the aortic valve. The conclusion is that this patient had an acute bacterial endocarditis of the aortic valve, with embolization to the aortic wall, mycotic-aneurysm formation and subsequent rupture.

It is probable that the source of the infection was the severe sore throat occurring early in the illness. Back pain was probably the result of the acute process in the aortic wall and cannot be attributed to actual rupture and retroperitoneal hemorrhage since this apparently occurred late in the course of the disease. We have seen a few cases in which an acute bacterial infection has been engrafted on the wall of the aorta at the site of severe atherosclerosis, with ultimate rupture at the site of mycotic-aneurysm formation.[1,2] In these cases no endocarditis was present. In this case the bacterial endocarditis was probably the source of infected embolus, but an independent engrafting of bacteria at the site of severe atherosclerosis cannot be excluded. Unfortunately, bacteriologic studies were not carried out.

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CASE 42392

PRESENTATION OF CASE

A twenty-nine-year-old gravida 1, para 1, housewife was admitted to the hospital because of metrorrhagia.

Seven weeks previously she noted a small amount of brownish vaginal discharge for two days when the normal menstrual period was expected. A week later there was an acute onset of steady, poorly localized lower abdominal pain that was more marked on the left side and not severe. There was diffuse tenderness in the lower abdomen. Pelvic examination revealed fresh blood in the vagina; the cervix appeared normal; the uterine fundus, which lay anteriorly, was slightly enlarged and tender; a tender, movable mass that measured 3 cm. in diameter was felt posteriorly in the left adnexa. On the next day pelvic examination showed no abnormalities, and normal menstrual bleeding was noted. Subsequently, there was vaginal spotting nearly every day requiring 1 or 2 pads daily. The abdominal pain subsided considerably. A course of Premarin for ten days caused a decrease in the amount of bleeding. Pelvic examination a week before entry showed tenderness and questionable thickening in the left vaginal vault.

Ten months previously a uterine dilatation and curettage was done at another hospital because of slight postmenstrual staining. After this procedure the menstrual cycles were normal. A cesarean section was performed four and a half years previously.

Physical examination revealed a well nourished woman in no distress. The abdomen was negative

except for a healed lower mid-line incision. Pelvic examination revealed a firm, rounded, movable mass measuring 4 cm. in diameter high in the left parametrium; the uterus lay anteriorly; the cervix and right adnexa were negative.

The temperature was 98.6°F., the pulse 76, and the respirations 14. The blood pressure was 116 systolic, 70 diastolic.

The urine was normal. Examination of the blood revealed a hemoglobin of 13 gm. per 100 ml. and a white-cell count of 6500. Cytologic examination of a vaginal smear for malignant cells was negative. An x-ray film of the abdomen was normal.

An operation was performed on the second hospital day.

Differential Diagnosis

Dr. George S. Richardson*: This woman of childbearing age had an illness of short duration, consisting of abnormal uterine bleeding and a left-sided adnexal mass associated with pain in the same region. It is difficult and probably fruitless to try to escape the conclusion that the mass was the patient's disease, causing both the pain and the bleeding. She had previously been well gynecologically speaking except that her only child had been born by cesarean section four and a half years previously and that she had had a dilatation and curettage for slight postmenstrual staining. I can think of no common reason for the cesarean section done so long before the present complaint and the present illness.

For the most part the indication for section is, first, disturbances in the mechanism of parturition only manifest at term and, secondly, some condition such as diabetes, in which section may be thought safer. Perhaps it is important to try to explain the subsequent childlessness. Had the difficulties been such that an attempt was made to sterilize her at the same time? Was the post-partum course complicated by enough pelvic infection to block the tubes? In any event she apparently resumed normal menstruation, and the dilatation and curettage ten months before admission succeeded in correcting the slight and probably functional increase in bleeding that she had then. This remains an assignment to account for the present illness of only seven weeks.

Was the bleeding on the basis of the hormonal abnormality? More specifically, was the mass in the left vault an ovary whose disturbed function had caused the bleeding — for example, a functioning tumor such as a granulosa-cell tumor or a follicle cyst? Either one of these may cause bleeding by producing sustained, but not necessarily elevated, levels of estrogen, which fluctuate enough to allow partial shedding of a proliferative endometrium that never changes completely. A similar mechanism has been evoked to explain metrorrhagia associated with pelvic inflammatory disease, with the notion that periovarian adhesions in some way prevent ovulation and allow cysts to form. This last would have the advantage of explaining the infertility, but if it was an old process, not the present pain.

Endometriosis is associated with pain, low fertility and, often, disturbed menstruation. Could the left-sided adnexal mass have been an endometrioma? Endometriosis, or at least the transplantation of endometrial tissue to ectopic sites, has been known to follow cesarean section. Could we fit this in too? Endometriosis, however, is usually associated with dysmenorrhea (in about two thirds of the cases), not mentioned here. Furthermore, we should expect a longer period of symptoms rather than the abrupt onset that this patient had.

Now, the thing that can happen abruptly to change the gynecological status of a woman in this age group is, of course, pregnancy. Could she have been undergoing spontaneous abortion associated with a painful corpus luteum? Perhaps the disappearance of the enlargement of the uterine fundus, no longer mentioned after the first examination done six weeks before entry, represented completion of the abortion while the corpus luteum anomalously persisted. This sequence of events, however, again does not fit the story. Granted that the corpus luteum of pregnancy is sometimes tender, it is not likely to be so as soon as this after the last normal menstruation; nor is there any reason why symptoms produced by it should coincide with abortion — nor any reason why abortion, if spontaneous, should be accompanied by pelvic pain and tenderness.

In conclusion, then, I believe that this patient's triad of metrorrhagia, pelvic pain and adnexal mass is best explained by ectopic pregnancy. To be sure, some features require explanation here as well, but we can take assurance from the knowledge that ectopic pregnancy is a highly variable disease and a great masquerader. The sequence of events, then, is that some time after the last normal period, eleven weeks before admission, the patient conceived, and the egg implanted ectopically in the left adnexa — most probably on the basis of frequency — in the intermediate portion of the left tube. This may have been due to old pelvic inflammatory disease or to an unsuccessful attempt at sterilization by tubal ligation, but it may just as well have occurred in the absence of any specific tubal abnormality. Implantation in the wall of the tube was then followed by tubal distention, with further thinning of the already thin wall, and the first episode of pain may have been caused by bleeding, resulting from trophoblastic invasion of one of the innumerable small vessels in this highly vascular area. The bleeding may have occurred into the lumen of the tube and then run out of the fimbriated end,

*Assistant in surgery, Massachusetts General Hospital.

with consequent pain in the pelvic peritoneum; or it may have occurred into the broad ligament, resulting in the tender thickening, which obscured the mass itself when the patient was examined one week before entry. In any event it subsided spontaneously, just as in other cases in which one or more episodes of minor bleeding and pain may precede a massive one. Furthermore, the bleeding episode may have destroyed the product of conception, converting it into a carneous mole within the tube. The latter theory gives us a pat explanation for the absence of symptoms and signs of pregnancy as well and is consistent with only the slight enlargement of the mass noted over a six-week observation period. The uterine bleeding, then, was produced by decidual shedding, as occasionally occurs in these cases. If the product of conception was destroyed there should have been abrupt and complete shedding accompanying hormonal withdrawal at that time, possibly in the form of an "endometrial cast." We cannot tell if this would have occurred or not, and if it were threatening to do so, the dosage with Premarin could have been enough to prevent it. It is quite possible that the fetus was still alive at the time of operation, in which case the absence of signs of pregnancy could have been the result of the relatively low titer of hormone.

The x-ray films and laboratory findings are noncontributory. It only remains to mention that the relatively normal hemoglobin is not inconsistent with the small amount of internal and external bleeding we may suppose this patient to have had.

Clinical Diagnosis

Ectopic (tubal) pregnancy.

Dr. George S. Richardson's Diagnosis

Ectopic (tubal) pregnancy.

Anatomical Diagnosis

Tubal pregnancy.

Pathological Discussion

Dr. Leonard Atkins: Dr. Russell, will you discuss the operative findings?

Dr. Paul S. Russell, Jr.: The operation consisted first of culdoscopy. Very little free blood was encountered on insertion of the instrument into the peritoneal cul-de-sac, and a good view of the uterus, both tubes and ovaries was achieved. The left tube was distinctly enlarged, forming a fusiform mass about 3 by 4 cm. in size, and was dark reddish blue. It lay free in the pelvis without remarkable adhesions and was considered to be typical of tubal ectopic pregnancy. The uterus was slightly enlarged. No other abnormality was found.

Laparotomy was accordingly done immediately, and the left tube removed.

Dr. Atkins: The fusiform mass, which was in the middle portion of the left fallopian tube, showed placental villi with considerable hemorrhage and necrosis.

Dr. Russell: The fairly small size of the mass, which was freely mobile within the pelvis, made it difficult to be sure of at first. This, together with the mild and intermittent character of the patient's symptoms, led us astray in the early management of the patient. The continued slow bleeding and pelvic tenderness, however, brought us back on the track. At no time, I am sure, had there been any appreciable bleeding.

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CORTISONE AS A TERATOGENIC AGENT

AT the Clinical Meeting of the American Medical Association last December, Ingalls[1] presented a clear and succinct review of the present knowledge of the causes and prevention of developmental defects. He pointed out the large number and variety of congenital defects that may be determined not by hereditary genetic factors but by events that occur during fetal development. A wide variety of stressful situations experienced by the mother during pregnancy may give rise to these congenital defects, the nature and extent of which depend on the character and severity of the stress and the stage of gestation — and hence of fetal development — when that stress occurs. Ingalls also summarized the results of extensive studies carried out at the Harvard School of Public Health, where a whole panorama of congenital defects has been produced, using hypoxia as a standard stress in gravid mice at different stages of gestation.

In human beings the importance of illness in the mother during pregnancy as a determining factor in the occurrence of congenital defects was forcefully called to the attention of the medical profession after Gregg,[2] in Australia, pointed out the relation between various congenital lesions and the occurrence of rubella in the mother during early pregnancy. Since that time, careful studies of many case records have amply confirmed and extended Gregg's observations and have revealed many other examples of infections and traumatic experiences in the mothers during pregnancy that may be related to developmental defects in the human offspring. Many of these defects have been duplicated by other types of stress in laboratory animals.

Among the developmental defects that have been reproduced in animals is cleft palate. Ingalls noted that this abnormality is produced in mice by several types of stress — exposure to x-rays, vitamin deficiency, cortisone intoxication and anoxia — provided that the immediate or delayed effects of the stress are operating when the two halves of the palate fuse; in the mouse this occurs on the fifteenth day of gestation.

The teratogenic effect of cortisone in particular has been investigated in both mice and rabbits, in both of which a high incidence of cleft palate without harelip has been produced by administration of cortisone to gravid females during the appropriate stage of pregnancy. Baxter and Fraser[3] produced cleft palate in 44 per cent of offspring of house mice, this lesion being very rare in this species. In different strains of mice they succeeded in producing the same defect with cortisone in 4 to 100 per cent of offspring, depending on the genotype of the mother and fetus. The dose of cortisone and the period of gestation during which the cortisone is begun are important factors, in addition to the genetic constitution of the

animals, in determining the frequency of occurrence of this defect.[4] In rabbits, among which the same defect — namely, cleft palate without harelip — is also rare, Fainstat[5] was able to produce this abnormality in 17 of 35 offspring of 7 does that were given cortisone intramuscularly during pregnancy.

These experimental observations take on new meaning in the light of a case recently reported by Harris and Ross.[6] In this case, the mother was given a trial of cortisone therapy for chronic idiopathic steatorrhea. The cortisone administration was begun during the eighth week of pregnancy, and the offspring, a full-term stillborn infant, was found to have a cleft palate without harelip. Since the development and closure of the palate in the human fetus takes place at about the time when the patient was receiving fairly large doses of cortisone, the possibility of a causal relation must be considered. The authors very properly call attention to the similarity between the experimental findings in animals and their case. They conclude that cortisone therapy should not be undertaken early in pregnancy. Because the pregnancy was not recognized early in their case, they point to the desirability of excluding the possibility of early pregnancy before administering cortisone to women of child-bearing age.

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FREEBOOTING SURGEONS

EVEN the buccaneers who sailed the western main, making free with the lofty galleons of Spain, were in certain ways as human as the rest of mankind. They had their aches and pains, their wounds and various injuries and their dyspeptic moments, and like honest seafarers before and since that day required a ship's surgeon to salve their sores, to set their bones, to bleed and purge and puke them. The one disease of sailors with which they apparently came little in contact was "Scorbutick," for they touched land often and fished and caught turtles as they went along.

An interesting account of some of these pirate surgeons has been contributed by Donald McDonald to *History Today*, appearing in the March issue of that magazine. In the period when these characters flourished, freebooting was piracy only according to the point of view, and privateering and marque and reprisal were legitimate enterprises; privateering an overt act of war, marque and reprisal just short of it. As the author states, harrying the sea routes of Spain had come by the sixteenth century to be an accepted practice, following the example set by Hawkins and Drake, and it was no more than natural that certain unscrupulous adventurers soon lost sight of the distinction between friend and foe.

To lend substance to the theory of honor existing among thieves the Confederacy of the Brethren of the Coast was formed in 1625. The brethren were to all purposes pirates — nondescript "but strongly sprinkled with graduates of Oxford and Cambridge, noblemen, priests, poets and naturalists and not least among them the surgeon, with his chest of medicaments and his salary of 250 pieces of eight."

One of the best known of these swashbuckling practitioners was an Irish-Scottish highlander of Huguenot descent named Lionel Wafer, Weaver, Weber, de la Wafer, Waffer or Wasser. Having served as a surgical apprentice on the *Great Anne* in 1677 he found himself after various vicissitudes practicing the healing art at Port Royal. Here he met with Captain Edward Cook and a Captain Lynch and in their company again went seafaring. His adventures included a march across the Isthmus of Panama to the Pacific, where a Spanish ship was seized and taken around the Horn. He spent three years in jail in Virginia, where he barely escaped the noose, surviving to die, presumably more or less comfortably in bed, in England, about 1705. He was said to have been "an amiable and keenly observant young man."

A product of this rough and ready school of surgery, Herman or Harman Coppinger, an Irishman, had sailed under Wafer as surgeon's mate. After many adventures Coppinger's conscience smote him; he turned honest and when last heard from was sailing as surgeon in a Portuguese vessel, on a legitimate errand.

A third member of this surgical brotherhood, one John Esquemeling, a Frenchman who wrote in Dutch and hated the English, went out in 1666 to the island of Tortuga as a servant in the West India Company of France. When the Spaniards forced the evacuation of the island, Esquemeling was sold along with the other chattels, eventually landing in the hands of a surgeon from whom he learned some portion of the art and from whom he eventually bought his freedom on a promissory note. Discouraged perhaps with this debt he entered into "the wicked order of the Pirates, or Robbers at Sea." He later wrote *Buccaneers of America*, in which he gave Sir Henry Morgan such an ill name that he was sued for libel and required to pay £200 damage and make a public apology.

The best known of the buccaneering doctors, however, was Thomas Dover, a bachelor of arts of St. Mary's Hall, in Oxford, and recipient of a degree in medicine from Caius College of Cambridge University. He was apprenticed to Sydenham and practiced

at Bristol until 1708, when he set sail on a privateering expedition around the world. The ships on this protracted foray were the *Duke* and the *Duchess*, under the leadership of William Dampier. Dover served in the *Duchess* as chief medical officer and second in command to Captain Woodes Rogers. According to Dampier's theory, Dover's temper was so bad that he was unlikely to secure enough followers for a mutiny.

One of the details of the voyage is well known — the call at the island of Juan Fernandez off the west coast of South America, where the original Robinson Crusoe, Alexander Selkirk, was found and removed after his solitary sojourn of four years and four months.

Dover had six junior surgeons under him, with whose aid he brought to an end an outbreak of plague among the crews. Treatment consisted of bleeding each victim "to 100 ounces" and the administration of dilute sulfuric acid by mouth. All but eight survived both the disease and the treatment.

After returning to England, Dover settled off the Strand, holding office hours at the Jerusalem Coffee Shop. In 1721 he became a licentiate of the College of Physicians, to which he was accustomed to refer as "that clan of prejudiced gentlemen." In 1773 he published *An Ancient Physician's Legacy to his Country*, containing among other remedies the prescription to which his name is still attached.

REMOVAL OF WARTS

Verruca vulgaris, the common wart, has again reared its ugly head, despite its plantar proclivities, and again in the highly selective columns of the *British Medical Journal*.[1] This is untimely, because the matter of these excrescences, so often associated with the common toad (*Bufo bufonidae*), ugly and venomous, and their dispersion, was supposed to have been settled in the *British Medical Journal* itself, in 1952 ("Difficult Wart Treated by Suggestion")[2] and in a running series of elucidations disposed through the pages of the *New England Journal of Medicine* in the following year.[3-7]

The patient, in the case described by Couper and Davies,[2] happened by chance alone to be a brass turner of Britain, and his lesion digital rather than plantar. Willing to try anything for relief, he submitted to suggestion and was cured in six weeks. Photographs taken before and after treatment attested the effectiveness of the method. Psychotherapy of the vulgar wart,[3] based largely on the methods employed by Huckleberry Finn and his collaborators, appeared anonymously in the *New England Journal of Medicine* in 1953. Prominent among the accessory substances of therapy were immersion of the affected part in spunk water and the burying, by the dark of the moon, at a crossroad, of half a bean with a dash of wart blood on it.

Branson and Rhea,[4] in the same issue of the *Journal*, prosaically scientific, cured plantar warts by the injection of novocain, under pressure, into the stratum germinativum at the base of the growth, regardless of the state of the moon. Grund,[6] in a communication to the editor, extolled the virtue of bismuth over that of novocain, the technic of the injection being similar, and Gilpatrick,[7] addressing himself also to the editor, disclaimed any especial fear of plantar warts, having taken them always in his stride and cured them out of hand by injection and fulguration.

Although charm and warts have never been closely identified, the revival of interest in the *British Medical Journal* occurs in the Any Questions? department under the title "Wart Charming," any resemblance to Prince Charming et al. being purely circumstantial. In answer to a question regarding the technic of wart charming the editor confesses that the process is not entirely understood. Technics, however, are both varied and ancient, the intention being to transfer the warts to some other person or animal or object. This may be a lump of raw beefsteak, which is buried at a crossroad at midnight under a full moon, having first been applied to the wart. No explanation is given why the ritual takes place in full moonlight in merrie England and by the dark of the moon along the Mississippi.

Sir Kenelm Digby, in the seventeenth century, recommended washing the hands by the light of the moon in a silver basin containing nothing but the moonlight. Other suggestions made by the editor of Any Questions? are the transference of the warts to slugs, toads or small stones. The stones, in the last instance, are then wrapped in an ivy leaf and thrown away, the warts transferring themselves to whoever picks the pebbles up. Hypnotism and small doses of x-radiation are other methods of charming warts, according to this source of information; equally effective is their purchase by one who must be a friend indeed.

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Lowell	October 5	Albert H. Brewster, M.D.
Gardner	October 8	Carter R. Rowe, M.D.
Lynn*	October 8	Daniel J. Killoran, M.D., and John J. Crowley, M.D.
Brockton	October 11	George W. Van Gorder, M.D.
Pittsfield	October 17	Edward J. Coughlin, Jr., M.D.
Worcester	October 19	John W. O'Meara, M.D.
Fall River	October 22	David S. Grice, M.D., and Arthur W. Trott, M.D.
Springfield	October 23	James D. Fisher, M.D.
Hyannis	October 25	Paul L. Norton, M.D.

Rheumatic-Fever Clinic	Dates
North Reading	October 2, 9, 16, 23, 30
Fitchburg	October 3, 10, 17, 24, 31

Plastic Clinic	Held	Consultant
Eastern Massachusetts	Semi-monthly	Bradford Cannon, M.D., and Joseph E. Murray, M.D.
Western Massachusetts	Monthly	Joseph M. Baker, M.D.

Physicians referring new patients to clinic should get in touch with the district health officer to make appointments. Patients are seen by appointment only.

*This clinic serves Lynn, Lynnfield, Saugus, Nahant, Revere, Chelsea, Everett and Winthrop. Referrals should be made directly to the Lynn Clinic.

COMMUNICABLE DISEASES IN MASSACHUSETTS FOR AUGUST, 1956

RÉSUMÉ

Disease	August 1956	August 1955	Seven-Year Median
Brucellosis	1	0	1
Chancroid	1	1	1
Chicken pox	188	154	154
Diphtheria	2	0	3
Dog bite	1588	1217	1238
Dysentery, bacillary	4	22	7
Encephalitis, infectious	8	3	3
German measles	118	49	74
Gonorrhea	140	201	201
Granuloma inguinale	0	0	0
Hepatitis, infectious	21	34	34
Lymphogranuloma venereum	0	0	1
Malaria	0	4	1
Measles	90	135	151
Meningitis, meningococcal	3	5	3
Meningitis, Pfeiffer bacillus	0	1	2
Meningitis, pneumococcal	2	2	0
Meningitis, staphylococcal	0	0	0
Meningitis, streptococcal	0	0	0
Meningitis, undetermined	13	6	5
Mumps	163	216	275
Poliomyelitis	33	1750	192
Salmonellosis	46	51	28
Scarlet fever	42	51	53
Syphilis	174	165	156
Trichinosis	1	1	3
Tuberculosis, pulmonary	173	195	186
Tuberculosis, other forms	11	14	13
Typhoid fever	1	1	2
Whooping cough	69	84	159

COMMENT

Diseases below the seven-year median were diphtheria, bacillary dysentery, infectious hepatitis, measles, mumps, poliomyelitis, scarlet fever and whooping cough.

During August infectious hepatitis was at the lowest level for this month since 1951.

Measles reached the lowest level for this month in the history of the State.

During August poliomyelitis reached the lowest level for this month since 1943.

Whooping cough reached the lowest level for this month in the history of the State.

Diseases above the seven-year median were chicken pox, infectious encephalitis, German measles and salmonellosis.

During August chicken pox was at the highest level for this month since 1951.

GEOGRAPHIC DISTRIBUTION OF CERTAIN DISEASES

The following diseases were reported from the communities named:

Actinomycosis: Foxboro, 2.

Brucellosis: Framingham, 1.

Diphtheria: Boston, 1; Wrentham, 1; total, 2.

Dysentery, amebic: Athol, 1; Worcester, 1; total, 2.

Dysentery, bacillary: Holyoke, 1; Revere, 1; Springfield, 1; Westwood, 1; total, 4.

Encephalitis, infectious: Boston, 1; Bourne, 1; Brockton, 1; Holyoke, 1; Rochester, 1; Weymouth, 3; total, 8.

Hepatitis, infectious: Arlington, 1; Beverly, 1; Boston, 3; Cambridge, 1; Chelsea Naval Hospital, 2; Lawrence, 1; Lynn, 1; Malden, 2; Peabody, 1; Pittsfield, 1; Reading, 1; Springfield, 2; Worcester, 4; total, 21.

Meningitis, meningococcal: Holyoke, 1; Melrose, 1; Westwood, 1; total, 3.

Meningitis, pneumococcal: West Springfield, 1; Worcester, 1; total, 2.

Meningitis, undetermined: Acton, 1; Avon, 1; Boston, 4; Lynnfield, 1; Medford, 2; Waltham, 1; Watertown, 1; Weymouth, 1; Worcester, 1; total, 13.

Poliomyelitis: Attleboro, 2; Boston, 2; Bourne, 2; Braintree, 1; Brockton, 3; Cambridge, 1; Douglas, 1; Fall River, 2; Fort Banks, 1; Lynn, 1; Lynnfield, 1; Melrose, 1; Montague, 2; Natick, 1; Needham, 1; Newburyport, 1; Salem, 1; Saugus, 1; Shrewsbury, 1; Springfield, 1; Waltham, 2; Worcester, 4; total, 33.

Psittacosis: Brockton, 1.

Salmonellosis: Abington, 2; Arlington, 3; Belmont, 1; Beverly, 1; Boston, 8; Chicopee, 1; Essex, 1; Everett, 3; Gardner, 1; Lincoln, 2; Ludlow, 1; Lynn, 4; Lynnfield, 1; Marblehead, 5; Marion, 1; Newton, 2; North Reading, 1; Peabody, 1; Revere, 1; Somerville, 1; Springfield, 2; Westwood, 1; Worcester, 2; total, 46.

Tetanus: Concord, 1.

Trichinosis: Boston, 1.

Typhoid fever: Boston, 1.

CORRESPONDENCE

STUDENT AMERICAN MEDICAL ASSOCIATION FOUNDATION

To the Editor: In the July 19 issue of the *Journal* the editorial, "House of Delegates," lists 22 important actions taken by the House of Delegates of the American Medical Association at its 1956 annual session. In the interest of accuracy I believe it should be reported to your readers that the proposal for a rotating scholarship fund for medical students as indicated in item No. 21 was not rejected but rather referred to the board of trustees for consideration and further action.

In this connection representatives of the official family of the Student American Medical Association appeared before the board of trustees of the American Medical Association on Friday, September 14, for the purpose of outlining the progress and plans of the newly established Foundation of the Student American Medical Association.

I hope that you can bring this correction to the attention of your readers and also wish to thank you in advance for any co-operation you can give the Association in the furtherance of its foundation.

Russell F. Staudacher
Executive Secretary
Student American Medical Association
Chicago

RUPTURE OF THE HEART

To the Editor: The article, "Rupture of the Heart after Myocardial Infarction," which appeared in the July 5 issue of the *Journal*, was a fine review of the subject. In purporting to be exhaustive in its extent, however, it failed to recognize certain single case reports that may be as important as certain larger series. This is particularly true regarding the statement, "Auscultatory findings have been noted in only three reports" (of rupture of the heart after myocardial infarction).

Strictly to keep the scientific record chronologic, just and accurate (and not at all to assuage the affront to my own ego by the omission of our single case report from among the 152 references cited), I should like to call attention to several facts.

Before our own unique experiences with spontaneous myocardial rupture, I was unable to find any reference in the English language to such auscultatory oddities other than in the 1922 paper of Reznikoff's, which Maher et al. mentioned (reference 10 in their review and reference 6 in our case report). In an article entitled "Spontaneous Rupture of the Heart Due to Myocardial Infarction" (*Am. J. Med.* 5:775, 1948), Dr. Drake and I wrote a minutely detailed description of the bedside appearance of the unfortunate patient whose left ventricle ruptured literally "before our eyes" (this being before the days of elective valvular surgery). Furthermore, we made the following notation:

> . . . no friction rub was heard before this spectacular episode but immediately after its inception an intense, grating pericardial rub was audible from the third left interspace down to the apex. Unfortunately, we had taken the stethoscope off the chest for a moment prior to the appearance of the pericardial rub to answer a question; so if rupture of the ventricle occurred at this instant (which we assume it did), we did not actually hear it . . .

For the very regrettable reason that I had removed my stethoscope momentarily, we thought, in reporting that case, that the title did not warrant an addition featuring the auscultatory findings. Subsequently, I have not believed that this extreme temperance (in case reporting) has been justified, particularly since it fails to give proper significance to the paper we wrote.

Although our auditory impressions were not as complete or extended as we should have liked, the fact remains that they *were* recorded honestly and without prejudice in the medical literature and that they *do* antedate those of Nuzun (1950) and Bishop and Logue (1950).

Precisely because much similar valuable clinical information (with valvular surgery in its infancy and lusty growth) was not readily available in cardiology textbooks at the time, I was moved to edit, *Clinical Cardiology*, which was published in May, 1953. It, of course, contains (P. 655) reference to our experience with the case mentioned above. Indeed, on the following page of the book, a photograph of the pathological specimen in Dr. George Geckeler's case of ante-mortem diagnosis of infarction of the interventricular septum, to which Maher et al. referred (reference 60), is reproduced. Finally, this book was reviewed, favorably, by Dr. Howard B. Sprague in the January 21, 1954, issue of the *Journal*.

FRANKLIN C. MASSEY, M.D.
Assistant Professor of Medicine and Chief, Heart Clinic
Hahnemann Medical College
Philadelphia

NOTICES

CHILDREN'S MEDICAL CENTER

Pediatric facilities for children will be officially recognized when the new Children's and Infants' Hospital Building of the Children's Medical Center is dedicated on October 5. Among the speakers for the occasion are President Nathan M. Pusey, of Harvard University, President James R. Killian, of Massachusetts Institute of Technology, and the Reverend Theodore P. Ferris.

Tours will be conducted during the afternoon, and the medical staff has prepared exhibits interesting to both medical and lay visitors.

The new main building will become the central building of the Children's Medical Center, housing patients of the Children's and Infants' Hospital, replacing obsolete accommodations for more than 200 patients.

UNIVERSITY OF VIRGINIA

The first annual Dudley Crofford Smith Lecture in Dermatology will be held at the University of Virginia, on Monday evening, October 29.

Dr. Walter C. Lobitz, Jr., assistant professor of hematology at Dartmouth Medical School, will talk on the subject "Wound Healing Following Experimental Injury in the Human Skin."

A reception will be held at the Farmington Country Club, and a portrait of the late Dr. Smith will be presented to the University.

NFIP GRANTS

The Division of Professional Education of the National Foundation for Infantile Paralysis has announced grants from March of Dimes funds to provide assistance to colleges, universities and professional agencies and associations. The purpose is to increase the number of qualified professional personnel, help improve standards of education and practice and provide specialized educational programs for professional persons concerned with care of patients. These grants are in addition to the fellowships announced in a previous issue.

Application should be made to:

Division of Professional Education
National Foundation for Infantile Paralysis
120 Broadway, New York 5, New York

AMERICAN BOARD OF OBSTETRICS AND GYNECOLOGY

The American Board of Obstetrics and Gynecology announces that the next scheduled examination (Part 1), written examination and review of case histories for all candidates will be held in various cities of the United States, Canada and military centers outside the continental United States on Friday, February 1, 1957.

Case reports are to be sent to the Secretary within thirty days upon receipt of notice of eligibility. Further information may be obtained from Dr. Robert L. Faulkner, Secretary, American Board of Obstetrics and Gynecology, 2105 Adelbert Road, Cleveland 6, Ohio.

SOCIETY MEETINGS AND CONFERENCES

SEPTEMBER 28 and 29. Mississippi Valley Medical Society and American Medical Writers' Association. Page 402, issue of August 23.
OCTOBER 1-31. Consultation Clinic for Crippled Children in Massachusetts. Page 626.
OCTOBER 3 and 10. Lahey Clinic Lectures. Page 489, issue of September 6.
OCTOBER 4, 5 and 6. Academy of Psychosomatic Medicine. Page 402, issue of August 23.
OCTOBER 5. Children's Medical Center. Notice above.
OCTOBER 5 and 6. New England Surgical Society. Page 489, issue of September 6.
OCTOBER 7, 8 and 9. New Hampshire and Vermont State Medical Societies. Page 304, issue of August 9.
OCTOBER 8-12. American Society of Anesthesiologists. Page 490, issue of September 6.
OCTOBER 8-13. International Cancer Cytology Congress. Page 104, issue of July 12.
OCTOBER 9-13. American Rhinologic Society. Page 490, issue of September 6.
OCTOBER 12. New England Rheumatism Society. Page 489, issue of September 6.

OCTOBER 15–17. American College of Gastroenterology. Page 539, issue of September 13.
OCTOBER 15–26. New York Academy of Medicine. Page 304, issue of August 9.
OCTOBER 17. Massachusetts Society of Examining Physicians. Page 584, issue of September 20.
OCTOBER 19 and DECEMBER 14, 1956, and FEBRUARY and APRIL, 1957. Massachusetts Society for Research in Psychiatry. Page 56, issue of July 5.
OCTOBER 29. University of Virginia. Page 627.
OCTOBER 30 and 31 and NOVEMBER 1. New England Postgraduate Assembly, Boston.
NOVEMBER 12–16. American Public Health Association. Page 402, issue of August 23.
NOVEMBER 14–22. Pan-Pacific Surgical Association. Page 490, issue of September 6.
NOVEMBER 18–22. Pan American Medical Association. Page 490, issue of September 6.

CALENDAR FOR THE WEEK BEGINNING THURSDAY, OCTOBER 4

THURSDAY, OCTOBER 4

*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*8:00–9:00 a.m. Surgical Grand Rounds. Dr. John Spellman and staff. Saint Elizabeth's Hospital.
*8:45–9:45 a.m. Cardiac Grand Rounds. Jimmy Fund Building, Children's Medical Center, 35 Binney Street.
*9:00–10:00 a.m. Surgical Rounds. Sherman Auditorium, Beth Israel Hospital.
*9:00–10:00 a.m. Arthritis Grand Rounds. Robert Breck Brigham Hospital.
*10:00–11:00 a.m. Combined Medical-Surgical Rounds. Sherman Auditorium, Beth Israel Hospital.
10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by Members and Guests of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*11:00 a.m.–12:00 m. Medical Grand Rounds. Dr. Sylvester McGinn and staff. Saint Elizabeth's Hospital.
*11:00 a.m.–12:00 m. Medical Staff Conference. Sherman Auditorium, Beth Israel Hospital.
*11:00 a.m.–12:30 p.m. Hand Clinic (Physical Medicine and Rehabilitation Service). Boston City Hospital.
*12:00 m. Clinicopathological Conference. Dr. Benjamin Castleman and associates. Pathology Amphitheater, Massachusetts General Hospital.
*12:00 m.–1:00 p.m. Surgical Staff Conference. Sherman Auditorium, Beth Israel Hospital.
*12:00 m.–1:00 p.m. Metabolism Conference. Stearns Auditorium, New England Center Hospital.
*12:15–1:15 p.m. Tumor Clinic. Dr. T. W. Botsford. Amphitheater, Peter Bent Brigham Hospital.
*3:00 p.m. Thoracic Conference. Bronchogenic Carcinoma. Dr. Harrison Black. Main Amphitheater, Peter Bent Brigham Hospital.
5:45 p.m. Medical Journal Club. Joslin Clinic (Cafeteria), New England Deaconess Hospital.

FRIDAY, OCTOBER 5

*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*8:00–9:00 a.m. Members and Guests of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*9:30–11:30 a.m. Medical and Surgical Grand Rounds. Drs. George W. Thorn and Francis D. Moore. Main Amphitheater, Peter Bent Brigham Hospital.
*10:00 a.m. Tuberculosis Surgical Clinic. South End Health Unit, 57 East Concord Street.
10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by Members and Guests of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*11:00 a.m.–12:30 p.m. Medical Grand Rounds. Stearns Auditorium, New England Center Hospital.
*12:00 m. Pediatric Grand Rounds. Thorndike Amphitheater, Boston City Hospital.
*12:00 m. Urological Conference. Dr. C. J. E. Kickham, presiding. Auditorium, Carney Hospital, Dorchester.
*12:00 m.–1:00 p.m. Gastrointestinal or Allergy Conference. Stearns Auditorium, New England Center Hospital.
*12:30–1:30 p.m. Surgical Grand Rounds. Stearns Auditorium, New England Center Hospital.
*1:30 p.m. Fertility and Endocrine Clinic. Free Hospital for Women, Brookline.
*1:30 p.m. Tumor Clinic. Mount Auburn Hospital, Cambridge.
*2:00–3:00 p.m. Pathology Conference. Dr. James Graham. Saint Elizabeth's Hospital.
*4:00–6:00 p.m. X-Ray Conference. Dr. Merrill C. Sosman. Stearns Auditorium, New England Center Hospital.
*4:00–10:00 p.m. Alcoholism Clinic. By appointment. Washingtonian Hospital, 41 Morton Street, Jamaica Plain.
*4:30 p.m. Neuroradiologic Conference. X-Ray Conference Room, New England Deaconess Hospital.

SATURDAY, OCTOBER 6

*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*8:30–10:00 a.m. Orthopedic Staff Conference. Boston City Hospital.
*8:30–10:00 a.m. Surgical Grand Rounds. Drs. Charles G. Child, III, A. J. A. Campbell and staff. First (Tufts) Surgical Service, New Cheever Amphitheater, Dowling Building, Boston City Hospital.
*9:00–10:00 a.m. Anesthesiology Conference. Dr. Benjamin Etsten. Anesthesia Laboratory, New England Center Hospital.
*9:30–11:00 a.m. Surgical House Officers' Conference. Second-Floor Conference Room, Carney Hospital, Dorchester.
*10:30 a.m. Teaching Ward Rounds. Ward South 2, Free Hospital for Women.
10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by Members and Guests of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*11:00 a.m.–12:00 m. Hematology Conference. Dr. William Dameshek. Stearns Auditorium, New England Center Hospital.

MONDAY, OCTOBER 8

*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by Members and Guests of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*11:00 a.m.–12:30 p.m. Staff Conference. Child Psychiatry. By appointment. Conference Room (Burnham 7), Massachusetts General Hospital.
*12:00 m.–1:00 p.m. Pediatric Clinicopathological Conference. Pratt Lecture Hall, Joseph H. Pratt Diagnostic Hospital.
*12:00 m.–1:00 p.m. Metabolism Conference. Dr. Schwartz. Stearns Auditorium, New England Center Hospital.
*12:15–1:15 p.m. Clinicopathological Conference. Main Amphitheater, Peter Bent Brigham Hospital.
*1:00 p.m. Alcoholism Clinic. Peter Bent Brigham Hospital.
*2:00–3:00 p.m. X-Ray Conference. Dr. William Carey. Saint Elizabeth's Hospital.
*3:00–4:00 p.m. Neuroradiologic Conference. Dr. Bertram Selverstone. Stearns Auditorium, New England Center Hospital.
*4:00 p.m. Clinicopathological Conference. Pathology Conference Room, Beth Israel Hospital.
*4:00–5:30 p.m. Anesthesiology Conference. Common Properties of the Opiates. Dr. Elia Lipschitz. Surgical Conference Room, Peter Bent Brigham Hospital.
*4:00–5:30 p.m. Anesthesiology Conference. Dr. Benjamin Etsten. Stearns Auditorium, New England Center Hospital.
*5:00–6:30 p.m. Anesthesia Group of the Lahey Clinic. Joslin Auditorium, New England Deaconess Hospital.
*7:00–9:00 p.m. Slide Seminar in Pathology. Dr. Edward T. MacMahon. Stearns Auditorium, New England Center Hospital.

TUESDAY, OCTOBER 9

*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*8:00–9:00 a.m. Medical Grand Rounds. Pathology Conference Room, Carney Hospital, Dorchester.
*10:30 a.m. Medical Grand Rounds. Main Conference Room (Ground Floor), Lemuel Shattuck Hospital.
10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by Members and Guests of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*12:00 m.–1:00 p.m. Pediatric Grand Rounds. Burnham Memorial Hospital for Children (Burnham 4), Massachusetts General Hospital.
*12:15–1:15 p.m. X-Ray Conference. Dr. Merrill Sosman. Main Amphitheater, Peter Bent Brigham Hospital.
*2:00–3:00 p.m. Hematology Conference. Dr. Mario Stefanini. Saint Elizabeth's Hospital.
*5:00 p.m. Surgical Journal Review. Mount Auburn Hospital, Cambridge.
*5:00–6:00 p.m. Service Meeting Followed by Clinical Conference (Medical, Surgical, Obstetric). Faulkner Hospital.

WEDNESDAY, OCTOBER 10

*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*8:00–9:00 a.m. Medical and Surgical Clinic on Diabetic Problems. Deaconess II, New England Deaconess Hospital.
*8:00–9:00 a.m. Surgical Grand Rounds. Auditorium, Carney Hospital, Dorchester.
*9:00–10:00 a.m. Surgical Grand Rounds. Massachusetts Memorial Hospitals.
10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by Members and Guests of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*11:00 a.m. Orthopedic Grand Rounds. Bigelow Amphitheater, White 3A, Massachusetts General Hospital.
*12:00 m.–1:00 p.m. Boston State Hospital Psychiatry Seminar. Reception Building Auditorium, 591 Morton Street, Dorchester.
*12:00 m.–1:00 p.m. Roentgen Diagnostic Conference. 5th-floor teaching unit, Beth Israel Hospital.
*12:00 m.–1:00 p.m. Neurology, Neurosurgery and Psychiatry Conference. Drs. John F. Sullivan, Justin Hope and Bertram Selverstone. Stearns Auditorium, New England Center Hospital.
*12:00 m.–1:00 p.m. Pediatric Medical-Surgical Rounds. Pratt Lecture Hall, Joseph H. Pratt Diagnostic Hospital.
*12:00 m.–1:00 p.m. Pediatric Clinicopathological Conference. Jimmy Fund Building, Children's Medical Center, 35 Binney Street.
*12:15 p.m. Vascular Rounds. Drs. Edward A. Edwards and Chilton Crane. D-Main, Peter Bent Brigham Hospital.
*12:30–1:30 p.m. Weekly Staff Review of Autopsies. Dr. William A. Meissner. Joslin Auditorium, New England Deaconess Hospital.
*1:00 p.m. Alcoholism Clinic. Peter Bent Brigham Hospital.
*1:00 p.m. Massachusetts General Hospital Hand Clinic. The Clinics of the Massachusetts General Hospital.
*2:00 p.m. Rectal Clinic. Peter Bent Brigham Hospital.
*2:00–3:00 p.m. Pediatric Conference for Practitioners. Jimmy Fund Building, Children's Medical Center, 35 Binney Street.
*4:00–5:30 p.m. Fracture Lecture. Boston City Hospital.
*4:00–6:00 p.m. Overbolt Thoracic Conference. Joslin Auditorium, New England Deaconess Hospital.
*6:00 p.m. Alcoholism Clinic. Peter Bent Brigham Hospital.
*6:00 p.m. Lahey Clinic Lecture. Obesity. Dr. Rosemary Murphy. Joslin Auditorium, New England Deaconess Hospital.

*Open to the medical profession.